IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent No. 5,116,863

Issued: May 26, 1992

Assignee: Kyowa Hakko Kogyo Co., Ltd.

Attention: BOX PATENT EXTENSION

CERTIFICATE OF MAILING BY EXPRESS MAIL UNDER 37 C.F.R. §1.10

I hereby certify that this correspondence is being deposited with the United States Postal Service as "Express Mail," Mailing Label No. EM246266075US in an envelope addressed to: Assistant Commissioner of Patents, Box Patent Extension, Washington, D.C. 20231 on this date:

Date: 2-13-97

Name: Jeannie Burke

Signature: Jeannie Burke

APPLICATION FOR EXTENSION
OF TERM UNDER 35 U.S.C. §156

Assistant Commissioner of Patents
BOX PATENT EXTENSION
Washington, D.C. 20231

Dear Sir:

Alcon Laboratories, Inc. ("Alcon") as authorized agent of the patent owner, Kyowa Hakko Kogyo Co., Ltd. ("Kyowa"), hereby applies for extension of the term of United States Patent No. 5,116,863

BACKGROUND

Alcon is the exclusive licensee of U.S. Patent No. 5,116,863 in the field of ophthalmology by virtue of a license agreement effective as of July 27, 1993. With the consent of Kyowa, Alcon applied for and received United States Food and Drug Administration (hereinafter "FDA") approval for the commercial marketing of a new ophthalmic drug product known as PATANOL™ (olopatadine hydrochloride ophthalmic solution) 0.1% which contains the hydrochloride salt of the sole compound claimed in that patent (i.e., 11-[(*Z*)-3-(Dimethylamino)propylidene-6,11-dihydrodibenz[b,e] oxepin-2-acetic

acid hydrochloride, also known as "olopatadine") as its sole active ingredient. The FDA granted Alcon's application for approval to market this product on December 18, 1996. This product is hereinafter referred to as "the approved product." Kyowa, which is the owner of record of U.S. Patent No. 5,116,863 and licensor of that patent to Alcon, has expressly authorized Alcon to submit this Application, as demonstrated by the accompanying Authorization and Power of Attorney document attached as Appendix A.

As explained below, it is believed that the '863 patent is eligible for an extension of term under the provision of 35 U.S.C. §156. Alcon has therefore submitted this Application for Extension of Term, in accordance with 35 U.S.C. §156 and the applicable Patent Office regulations (i.e., 37 C.F.R. §§ 1.710, et. seq.).

ELIGIBILITY

United States Patent No. 5,116,863 is eligible for extension under the provisions of 35 U.S.C. §156(a) and 37 C.F.R. §§1.710 and 1.720. The criteria for eligibility are set forth below:

(1) the '863 patent claims the active ingredient contained in the approved product;

(2) the term of the '863 patent has not expired prior to submission of this Application;

(3) the term of the '863 patent has never been previously extended;

(4) no other patent has been extended based on the regulatory review period for the approved product;

(5) the approved product has been subject to a regulatory review period of the type defined in 35 U.S.C. §156(g)(1)(A);

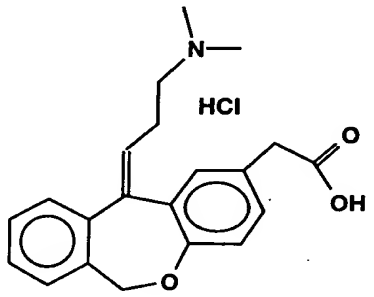
(6) the permission for commercial marketing or use of the approved product resulting from the regulatory review period is the first permitted commercial marketing or use of any human drug product containing the active ingredient contained in the approved product (i.e., olopatadine); and

(7) an application for extension of term meeting the requirements of 35 U.S.C. §156(d) has been submitted within the period specified in 35 U.S.C. §156(d)(1).

APPLICATION

In accordance with the requirements of 35 U.S.C. §156(d) and 37 C.F.R. §§ 1.730 and 1.740, Alcon presents the following information. The paragraph numbers utilized below correspond to the paragraph numbers under subparagraph (a) of 37 C.F.R. §1.740:

(1) The approved product is a sterile ophthalmic solution which contains olopatadine (0.1%) as its sole active ingredient. Olopatadine has the following structural formula:



Further details concerning this compound are presented in the USP Dictionary of USAN and International Drug Names; a copy of page 515 of that publication is attached as Appendix B. Further details concerning the approved product are presented in the FDA-approved package insert; a copy of that insert is attached as Appendix C.

(2) The regulatory review occurred under Sections 505(i) and 505(b) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 et. seq.)

(3) The approved product received FDA approval under Section 505(b) of the Federal Food, Drug, and Cosmetic Act on December 18, 1996. A copy of the approval letter is attached as Appendix D.

(4) As stated above, the active ingredient of the approved product is olopatadine. This compound has not been previously approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

(5) This Application is being submitted within the sixty (60) day period specified in 35 U.S.C. §156(d)(1) and 37 C.F.R. §1.720(f), which period expires on February 18, 1997.

(6) The patent for which an extension is being sought is United States Patent No. 5,116,863. This patent was issued to Etsuo Oshima; Toshiaki Kumazawa; Shizuo Otaki; Hiroyuki Obase; Kenjo Ohmori; Hidee Ishii; Haruhiko Manabe; Tadafumi Tamura; and Katsuichi Shuto on May 26, 1992, and will expire on May 26, 2009.

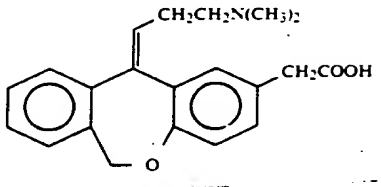
(7) A copy of United States Patent No. 5,116,863 in the form of a cut-up copy wherein only a single column is reproduced on each page is attached as Appendix E.

(8) No reexamination certificate, disclaimer or certificate of correction has been issued in connection with United States Patent No. 5,116,863. The first maintenance fee has been paid. A copy of the first Maintenance Fee Statement is attached as Appendix F.

(9) United States Patent No. 5,116,863 claims the active ingredient, olopatadine. Olopatadine is the active ingredient of the approved product. As indicated in the package insert (see Appendix C, page 1), the approved product is indicated for the temporary prevention of itching of the eye due to allergic conjunctivitis.

The '863 patent contains three claims, all of which read on the approved product. Claim 1 of the '863 patent reads as follows:

1. A dibenz[b,e]oxepin compound in cis form having the formula



and pharmaceutically acceptable salts thereof.

Olopatadine is the hydrochloride salt of the recited compound.

Claim 2 of the '863 patent reads as follows:

2. A compound according to claim 1, wherein said salt is selected from the group consisting of acid addition salt, metal salt, ammonium salt, organic amine addition salt, and amino acid addition salt.

Olopatadine is the hydrochloride salt of the recited compound. The hydrochloride salt is an acid addition salt.

Claim 3 of the '863 patent reads as follows:

3. A pharmaceutical composition comprising a pharmaceutical carrier and as an active ingredient, an effective amount of a dibenz[b,e]oxepin compound defined in claim 1.

The approved product contains an effective amount of olopatadine as the active ingredient and a pharmaceutical carrier.

Relevant Dates and Information pursuant to 35 U.S.C. §156(g)

(10) The relevant dates and information specified in 35 U.S.C. §156(g) are as follows:

(a) IND 44,216

The investigational new drug ("IND") application was filed on December 21, 1993. The IND application was assigned serial number 44,216. The effective date of the IND application was January 20, 1994.

(b) NDA 20-688

The new drug application ("NDA") was submitted on January 29, 1996. The NDA was assigned serial number 20-688. The NDA was approved on December 18, 1996.

Brief Description of Activities During the Regulatory Review Period

(11) The activities undertaken by Alcon during the regulatory review periods identified in paragraph (10) above were as follows:

(a) 12/21/93 - 12/20/94

Investigational New Drug Application No. 44,216 (hereafter "IND") was submitted to FDA under Section 505(i) of the Federal Food, Drug and Cosmetic Act on December 21, 1993. The notice for exemption became effective on January 20, 1994. A Phase I clinical safety study was then initiated with the first applications of the approved product taking place on January 20, 1994. In connection with this safety study and additional clinical studies, informational and protocol amendments were submitted to the FDA in January, February, March, April, June, July, August, November and December 1994. Two six-month ocular irritation and systemic safety studies were initiated: one in rabbits in February 1994 and one in primates in December 1994. Two multidose ocular clinical safety studies were initiated: one in Japan in February 1994 and one in the U.S. in June 1994. Three pivotal clinical studies to establish safety and efficacy were initiated on the following months: March 1994, August 1994 and October 1994. In addition, a meeting was held with FDA in May 1994 to discuss clinical requirements. This was followed by two teleconferences to further discuss clinical design and requirements (June 1994 and August 1994). Stability studies on the clinical formulation were initiated in July 1994.

(b) 12/21/94-12/90/95

Annual IND Progress Report No. 1 was submitted to the FDA. Informational and protocol amendments were submitted to the FDA in

January, February, March, April, May, June, July, August, October 1995. A long term safety study in adults and pediatric patients was initiated in February 1995. A teleconference to discuss clinical plan for future studies was held in March 1995. An end-of-Phase II meeting was held with the FDA in May 1995. A special exploratory clinical pharmacology study to determine tryptase levels in tears was initiated in October 1995. Animal safety studies were ongoing as were chemistry, manufacturing and controls studies. An analysis of the primary stability data was prepared to support the NDA filing.

(c) 12/21/95-12/20/96

Annual IND Progress Report No. 2 was submitted to the FDA. A New Drug Application (No. 20-688, hereinafter "NDA") was submitted on January 26, 1996. Amendments to the NDA and responses to FDA reviewers' requests were submitted in March, April, May, June, July, August, September, November and December 1996. The NDA was approved on December 18, 1996.

(d) Summary

The testing phase, beginning in January 1994, was characterized by continuous and uninterrupted clinical safety and efficacy studies through the time of the NDA filing on January 26, 1996. Subsequent to the NDA filing, Alcon continuously and diligently sought approval of its NDA covering the approved product. There were no periods between December 21, 1993 and December 18, 1996 that Alcon did not actively pursue approval from the FDA for commercial marketing of the approved product.

Statement of Applicant's Opinion Concerning Eligibility for an Extension and the Length of the Extension

(12) In the opinion of Alcon, United States Patent No. 5,116,863 is eligible for an extension of 571 days. The length of the extension was calculated as follows:

(a) IND Period

The IND period began on December 21, 1993, and ended on January 28, 1996. The IND period therefore included a total of 768 days. One-half of this total is 384 days.

(b) NDA Period

The NDA period began on January 29, 1996, and ended on December 18, 1996. The NDA period therefore included a total of 325 days.

(c) Total Regulatory Review Period

The regulatory review period for purposes of patent term extension was 709 days (i.e., 384 days plus 325 days).

(d) Limitation on Extension

Under the provision of 35 U.S.C. §156(c)(3), the term of a patent remaining after the date of product approval cannot exceed

fourteen (14) years. In the present case, this means that the term of the '863 patent cannot be extended beyond December 18, 2010. Therefore, it is the opinion of Applicant that only 571 of the 709 regulatory review period days available for patent extension can be utilized.

(13) Alcon hereby acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension requested herein.

(14) The accompanying Transmittal Letter requests that the $1,090.00 fee required by 37 C.F.R. §1.20(j) be charged to Deposit Account No. 01-0682.

(15) Alcon requests that all correspondence and inquiries in connection with this Application be directed to the following individual:

Patrick M. Ryan
Patent Department, Q-148
Alcon Laboratories, Inc.
6201 South Freeway
Fort Worth, Texas 76134
Phone: (817) 551-3066
Fax: (817) 551-4610

(16) A certified duplicate of this Application is being filed herewith.

(17) A Declaration meeting the requirements of 37 C.F.R. §1.740(b) is attached.

Based on the foregoing, it is believed that United States Patent No. 5,116,863 is entitled to an extension of 571 days. An official notice to that effect in the form of a certificate of extension is respectfully requested.

Respectfully submitted,

ALCON LABORATORIES, INC.

Date February 13, 1997

By Patrick M. Ryan
Patrick M. Ryan
Registration No. 36,263

Address for Correspondence:
Patrick M. Ryan
Patent Department, Q-148
Alcon Laboratories, Inc.
6201 South Freeway
Fort Worth, Texas 76134

Phone: (817) 551-3066

DECLARATION

This Application is submitted pursuant to extension of the term of United States Patent No. 5,116,863. The undersigned, as agent for Kyowa Hakko Kogyo Co., Ltd. ("Kyowa"), the owner of said patent, hereby declares:

THAT I am a patent attorney authorized to practice before the Patent and Trademark Office and authorized to act on behalf of Kyowa, owner of United States Patent No. 5,116,863, to apply for extension of the term of such patent;

THAT I have reviewed and understand the contents of the attached Application papers consisting of a twelve page Application, and Appendices A-F thereto;

THAT I believe United States Patent No. 5,116,863 is subject to extension pursuant to 35 U.S.C. §156 and 37 C.F.R. §1.710;

THAT I believe an extension of 571 days is fully justified under 35 U.S.C. §156 and the applicable regulations;

That I believe United States Patent No. 5,116,863 meets the conditions for extension of the term of a patent, as set forth in 37 C.F.R. §1.720; and

THAT all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this Application and any extension of United States Patent No. 5,116,863.

ALCON LABORATORIES, INC.

Date February 13, 1997

By Patrick M. Ryan

Patrick M. Ryan
Registration No. 36,263
Senior Patent Counsel

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent No. 5,116,863

Issued: May 26, 1992

Assignee: Kyowa Hakko Kogyo Co., Ltd.

Attention: BOX PATENT EXTENSION

CERTIFICATE OF MAILING BY EXPRESS MAIL

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as "Express Mail," Mailing Label No. EM246266075US in an envelope addressed to: Assistant Commissioner of Patents, Box Patent Extension, Washington, D.C. 20231 on this date:

2-13-97
Date

Jeannie Burke
Jeannie Burke

TRANSMITTAL OF FEE UNDER 37 C.F.R. §1.20(j)

Assistant Commissioner of Patents
Box Patent Extension
Washington, D.C. 20231

Dear Sir:

An application for extension of the term of the above-identified patent has been filed herewith on behalf of Kyowa Hakko Kogyo Co., Ltd., the owner of U.S. Patent No. 5,116,863, by the exclusive licensee Alcon Laboratories, Inc. Please charge the $1,090.00 fee required under 37 CFR. §§1.740(a)(14) and 1.20(j) to Deposit Account No. 01-0682. A duplicate of this paper is attached.

Respectfully submitted,

ALCON LABORATORIES, INC.

February 13, 1997
Date

Patrick M. Ryan
Patrick M. Ryan
Registration No. 36,263

Address for Correspondence:
Patent Department Q-148
Alcon Laboratories, Inc.
6201 South Freeway
Fort Worth, Texas 76134
(817) 551-3066
Docket No. L.A. 93-033

CERTIFICATION

I hereby certify that the attached papers are duplicates of the accompanying papers consisting of a twelve page document titled "APPLICATION FOR EXTENSION OF TERM UNDER 35 U.S.C. §156," and Appendices A-F thereto, and a Declaration meeting the requirements of 37 C.F.R §1.740(b).

Date: February 13, 1997

Patrick M. Ryan

Patrick M. Ryan
Registration No. 36,263

APPENDIX A

Authorization and Power of Attorney

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent No. 5,116,863
Issued: May 26, 1992

AUTHORIZATION AND POWER OF ATTORNEY

Assistant Commissioner of Patents
Box Patent Extension
Washington, D.C. 20231

Dear Sir:

Kyowa Hakko Kogyo Co., Ltd., owner of the entire right, title, and interest in U.S. Patent No. 5,116,863 by assignment recorded at reel 4674, frame 472-473, through its duly appointed officer hereby authorizes ALCON LABORATORIES, INC. of Fort Worth, Texas, to apply for extension of the term of U.S. Patent 5,116,863, on behalf of the patent owner Kyowa Hakko Kogyo Co., Ltd. Power of attorney to prosecute the application for extension is granted to:

Patrick M. Ryan, Reg. No. 36,263, patent counsel for Alcon Laboratories, Inc., and Robert L. Price, Reg. No. 22,685, of Lowe, Price, LeBlanc & Becker.

Correspondence should be mailed to:

Patrick M. Ryan
Alcon Laboratories, Inc.
Patent Department - Q-148
6201 South Freeway
Fort Worth, Texas 76134

February 7, 1997
Date

Tetsuo Oka
Name: Tetsuo Oka

Title: Senior Managing Director
Kyowa Hakko Kogyo Co., Ltd.

APPENDIX B

A copy of page 515 from USP Dictionary of USAN and International Drug Names

The authorized list of established names for drugs in the United States of America

USP Dictionary

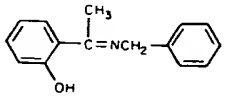
of USAN and International Drug Names

1997

Published in accordance with the directions of the Nomenclature Committee of the USP Committee of Revision, with the cooperation of the United States Adopted Names Council

U.S. Pharmacopeia
12601 Twinbrook Parkway, Rockville, MD 20852

Oletimol. $C_{15}H_{15}NO$. 225.29. *o*-(*N*-Benzylacetimidoyl)phenol. *CAS-5879-67-4*. INN; BAN.



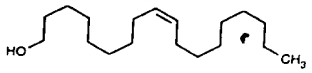
Oleum Caryophylii — *See* Clove Oil.

Oleum Gossypii Seminis — *See* Cottonseed Oil.

Oleum Maydis — *See* Corn Oil.

Oleum Ricini — *See* Castor Oil.

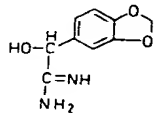
Oleyl Alcohol (oh lay′ il). NF. $C_{18}H_{36}O$. 268.49. (1) 9-Octadecen-1-ol, (*Z*)-; (2) (*Z*)-9-Octadecen-1-ol. *CAS-143-28-2*. *Pharmaceutic aid (emulsifying agent); pharmaceutic aid (emollient)*. Witcohol 85 (Witco); Witcohol 90 (Witco)



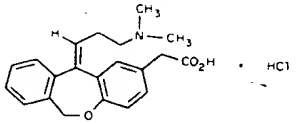
Olive Oil. NF. *CAS-8001-25-0*. JAN. *Pharmaceutic aid*.

Olivomycin. Antibiotic obtained from cultures of *Actinomyces olivoreticuli*, or the same substance obtained by any other means. *CAS-11006-70-5*. INN; MI.

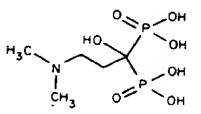
Olmidine. $C_9H_{10}N_2O_3$. 194.19. 3,4-(Methylenedioxy)mandelamidine. *CAS-22693-65-8*. INN; DCF.



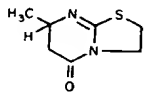
Olopatadine Hydrochloride *[1995]* (oh loe pa ta′ deen). $C_{21}H_{23}NO_3.HCl$. 373.88. [Olopatadine is INN.] (1) Dibenz[*b*,*e*]oxepin-2-acetic acid, 11-[3-(dimethylamino)-propylidene]-6,11-dihydro-, hydrochloride, (*Z*)-; (2) 11-[(*Z*)-3-(Dimethylamino)propylidene]-6,11-dihydrodibenz[*b*,*e*]oxepin-2-acetic acid, hydrochloride. *CAS-140462-76-6; CAS-113806-05-6* [olopatadine]. *Anti-allergic*. (Kyowa Hakko Kogyo Co., Ltd., Japan) ✧*KW4679; ALO4943A*



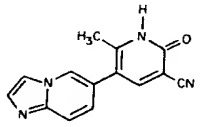
Olpadronic Acid. $C_5H_{15}NO_7P_2$. 263.12. [3-(Dimethylamino)-1-hydroxypropylidene]diphosphonic acid. *CAS-63132-39-8*. INN.



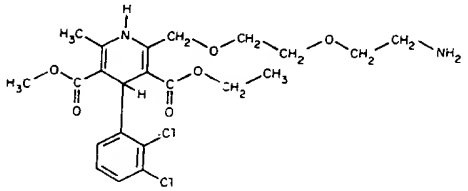
Olpimedone. $C_7H_{10}N_2OS$. 170.24. (±)-2,3,6,7-Tetrahydro-7-methyl-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one. *CAS-39567-20-9*. INN.



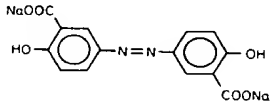
Olprinone. $C_{14}H_{10}N_4O$. 250.26. 1,2-Dihydro-5-imidazo[1,2-*α*]pyridin-6-yl-6-methyl-2-oxonicotinonitrile. *CAS-106730-54-5*. INN.



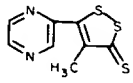
Olradipine. $C_{22}H_{28}Cl_2N_2O_6$. 487.38. 3-Ethyl 5-methyl (±)-2-[[2-(2-aminoethoxy)ethoxy]methyl]-4-(2,3-dichlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate. *CAS-115972-78-6*. INN.



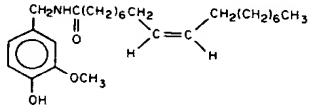
Olsalazine Sodium *[1987]* (ole sal′ a zeen). $C_{14}H_8N_2Na_2O_6$. 346.21. [Olsalazine is INN and BAN.] (1) Benzoic acid, 3,3′-azobis[6-hydroxy-, disodium salt; (2) C. I. Mordant Yellow 5, disodium salt; (3) Disodium 5,5′-azodisalicylate. *CAS-6054-98-4; CAS-15722-48-2* [olsalazine]. *Anti-inflammatory (gastrointestinal)*. Dipentum (Pharmacia) *[Names previously used: Sodium Azodisalicylate; Azodisal Sodium.]* ✧*CJ 91B*



Oltipraz. $C_8H_6N_2S_3$. 226.35. 4-Methyl-5-(pyrazinyl)-3*H*-1,2-dithiole-3-thione. *CAS-64224-21-1*. INN.



Olvanil *[1986]* (ole′ va nil). $C_{26}H_{43}NO_3$. 417.64. (1) 9-Octadecenamide, *N*-[(4-hydroxy-3-methoxyphenyl)methyl]-, (*Z*)-; (2) *N*-Vanillyloleamide. *CAS-58493-49-5*. INN. *Analgesic*. ✧*NE-19550*



OM-977. Code designation for Etaminile.

Omadine MDS. Olin brand of Bispyrithione Magsulfex.

OMDS. Code designation for Dipyrithione.

Omega-3 Marine Triglycerides. [Docosahexent and Icosapent are INN.] A mixture of the triglycerides of the fatty acids from marine fish containing the equivalent of about 18% of

† Brand name formerly used, and/or firm no longer concerned with this product.

APPENDIX C

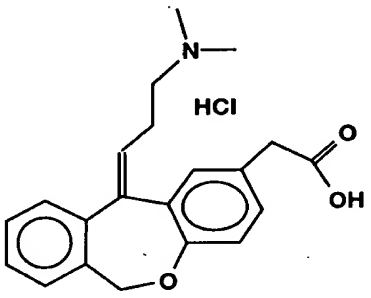
A copy of the FDA-approved package insert for the approved product

PATANOL™

(olopatadine hydrochloride ophthalmic solution) 0.1%

DESCRIPTION

PATANOL™ (olopatadine hydrochloride ophthalmic solution) 0.1% is a sterile ophthalmic solution containing olopatadine, a relatively selective H_1-receptor antagonist and inhibitor of histamine release from the mast cell for topical administration to the eyes. Olopatadine hydrochloride is a white, crystalline, water-soluble powder with a molecular weight of 373.88. The chemical structure is presented below:



Chemical Name: 11-[(Z)-3-(Dimethylamino)propylidene]-6-11-dihydrodibenz[b,e] oxepin-2-acetic acid hydrochloride

Each mL of PATANOL (olopatadine hydrochloride ophthalmic solution) 0.1% contains: **Active:** 1.11 mg olopatadine hydrochloride equivalent to 1 mg olopatadine. **Preservative:** benzalkonium chloride 0.01%. **Inactives:** dibasic sodium phosphate; sodium chloride; hydrochloric acid/sodium hydroxide (adjust pH); and purified water. DM-00

CLINICAL PHARMACOLOGY

Olopatadine is an inhibitor of the release of histamine from the mast cell and a relatively selective histamine H_1-antagonist that inhibits the *in vivo* and *in vitro* type 1 immediate hypersensitivity reaction. Olopatadine is devoid of effects on alpha-adrenergic, dopamine, muscarinic type 1 and 2, and serotonin receptors.

Following topical ocular administration in man, olopatadine was shown to have low systemic exposure. Two studies in normal volunteers (totaling 24 subjects) dosed bilaterally with olopatadine 0.15% ophthalmic solution once every 12 hours for 2 weeks demonstrated plasma concentrations to be generally below the quantitation limit of the assay (<0.5 ng/mL). Samples in which olopatadine was quantifiable were typically found within 2 hours of dosing and ranged from 0.5 to 1.3 ng/mL. The half-life in plasma was approximately 3 hours, and elimination was predominantly through renal excretion. Approximately 60-70% of the dose was recovered in the urine as parent drug. Two metabolites, the mono-desmethyl and the N-oxide, were detected at low concentrations in the urine.

Results from conjunctival antigen challenge studies demonstrated that PATANOL (olopatadine hydrochloride ophthalmic solution) 0.1%, when subjects were challenged with antigen both initially and up to 8 hours after dosing, was significantly more effective than its vehicle in preventing ocular itching associated with allergic conjunctivitis.

INDICATIONS AND USAGE

PATANOL (olopatadine hydrochloride ophthalmic solution) 0.1% is indicated for the temporary prevention of itching of the eye due to allergic conjunctivitis.

CONTRAINDICATIONS

Hypersensitivity to any component of this product.

WARNINGS

For topical use only. Not for injection. Patients should be instructed not to instill PATANOL™ (olopatadine hydrochloride ophthalmic solution) 0.1% while wearing contact lenses.

PRECAUTIONS

Information for Patients: To prevent contaminating the dropper tip and solution, care should be taken not to touch the eyelids or surrounding areas with the dropper tip of the bottle. Keep bottle tightly closed when not in use.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Olopatadine administered orally was not carcinogenic in mice and rats in doses up to 500 mg/kg/day and 200 mg/kg/day, respectively. Based on a 40 µl drop size, these doses were 78,125 and 31,250 times higher than the maximum recommended ocular human dose (MROHD). No mutagenic potential was observed when olopatadine was tested in an *in vitro* bacterial reverse mutation (Ames) test, an *in vitro* mammalian chromosome aberration assay or an *in vivo* mouse micronucleus test. Olopatadine administered to male and female rats at oral doses of 62,500 times MROHD level resulted in a slight decrease in the fertility index and reduced implantation rate; no effects on reproductive function were observed at doses of 7,800 times the maximum recommended ocular human use level.

Pregnancy: Pregnancy Category C. Olopatadine was found not to be teratogenic in rats and rabbits. However, rats treated at 600 mg/kg/day, or 93,750 times the MROHD and rabbits treated at 400 mg/kg/day, or 62,500 times the MROHD, during organogenesis showed a decrease in live fetuses. There are, however, no adequate and well controlled studies in pregnant women. Because animal studies are not always predictive of human responses, this drug should be used in pregnant women only if the potential benefit to the mother justifies the potential risk to the embryo or fetus.

Nursing Mothers: Olopatadine has been identified in the milk of nursing rats following oral administration. It is not known whether topical ocular administration could result in sufficient systemic absorption to produce detectable quantities in the human breast milk. Nevertheless, caution should be exercised when PATANOL (olopatadine hydrochloride ophthalmic solution) 0.1% is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in pediatric patients below the age of 3 years have not been established.

ADVERSE REACTIONS

Headaches were reported at an incidence of 7%. The following additional ocular and nonocular adverse reactions were reported at an incidence of less than 5%:

Ocular: Burning or stinging, dry eye, foreign body sensation, hyperemia, keratitis, lid edema, and pruritis.

Nonocular: Asthenia, cold syndrome, pharyngitis, rhinitis, sinusitis, and taste perversion.

DOSAGE AND ADMINISTRATION

The recommended dose is one to two drops in each affected eye two times per day at an interval of 6 to 8 hours.

HOW SUPPLIED

PATANOL (olopatadine hydrochloride ophthalmic solution) 0.1% is supplied as follows: 5, 10 and 15 mL in plastic DROP-TAINER® dispensers.

5 mL: **NDC** 0065-0271-05
10 mL: **NDC** 0065-0271-10
15 mL: **NDC** 0065-0271-15

Storage:

Store at 39°F to 86°F (4°C to 30°C).

Caution:

Federal (USA) law prohibits dispensing without prescription.

Alcon®
OPHTHALMIC
ALCON LABORATORIES, INC.
Fort Worth, Texas 76134 USA

January 1997

APPENDIX D

FDA Approval Letter of December 18, 1996

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-688

Alcon Laboratories, Inc.
Attention: Susan H. Caballa
Associate Director, Regulatory Affairs
6201 South Freeway
Fort Worth, Texas 76134-2099

DEC 18 1996

Dear Ms. Caballa:

Please refer to your new drug application dated January 26, 1996, received January 29, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Patanol (olopatadine hydrochloride ophthalmic solution) 0.1%.

We acknowledge receipt of your submissions dated March 8 and 12, April 2 and 19, May 28, June 17 (two), July 3, 10, 18, 22, and 24, August 1, 12, 16, and 26, September 6 and 17, 1996, November 1, 13, and 22, and December 13, 1996.

This new drug application provides for the temporary prevention of itching of the eye due to allergic conjunctivitis.

We have completed the review of this application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling in the submission dated December 13, 1996, with the following revisions. Accordingly, the application is approved effective on the date of this letter.

The revisions are as follows:

1. The word "olopatadine," in the second sentence of the second paragraph of the CLINICAL PHARMACOLOGY section, should not be capitalized.

2. Please revise the last sentence in the CLINICAL PHARMACOLOGY section to read, "Results from conjunctival antigen challenge studies demonstrated that PATANOL (olopatadine hydrochloride ophthalmic solution) 0.1%, when subjects were challenged with antigen both initially and up to 8 hours after dosing, was significantly more effective than its vehicle in preventing ocular itching associated with allergic conjunctivitis."

3. Please revise the first two sentences of the Carcinogenesis, Mutagenesis, Impairment of Fertility subsection of the PRECAUTIONS section to read, "Olopatadine administered orally was not carcinogenic in mice and rats in doses up to 500 mg/kg/day and 200 mg/kg/day, respectively. Based on a 40 µL drop size, these doses were 78,125 and 31,250 times higher than the maximum recommended ocular human dose (MROHD)."

The final printed labeling (FPL) must be identical to the draft labeling submitted on December 13, 1996, with the revisions noted above. Marketing the product with FPL that is not identical to this revised draft labeling may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-688. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products and two copies of both the promotional material and the package insert directly to:

Division of Drug Marketing, Advertising and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

In addition, we acknowledge the commitment made in your August 16, 1996, submission to conduct a Phase 4 study to provide further safety and efficacy data on Patanol 0.1% from a subject sample which is more broadly representative of U.S. demographics with respect to ethnic origin (80% Caucasian, 20% non-Caucasian).

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Joanne M. Holmes, M.B.A., Project Manager, at (301) 827-2090.

Sincerely yours,

MWeintraub 12/18/96

Michael Weintraub, M.D.
Director
Office of Drug Evaluation V
Center for Drug Evaluation and Research

APPENDIX E

A cut-up copy of United States Patent No. 5,116,863

United States Patent [19]

Oshima et al.

[54] **DIBENZ[B,E]OXEPIN DERIVATIVE AND PHARMACEUTICAL COMPOSITIONS THEREOF**

[75] Inventors: **Etsuo Oshima; Toshiaki Kumazawa; Shizuo Otaki; Hiroyuki Obase,** all of Shizuoka; **Kenji Ohmori,** Mishima; **Hidee Ishii,** Shizuoka; **Haruhiko Manabe,** Shizuoka; **Tadafumi Tamura,** Shizuoka; **Katsuichi Shuto,** Shizuoka, all of Japan

[73] Assignee: **Kyowa Hakko Kogyo Co., Ltd.,** Tokyo, Japan

[21] Appl. No.: **20,900**

[22] Filed: **Mar. 2, 1987**

[30] **Foreign Application Priority Data**

Mar. 3, 1986 [JP] Japan 61-45676

[51] **Int. Cl.**[5] **A61K 31/335;** C07D 313/12

[52] **U.S. Cl.** **514/450;** 548/215; 548/525; 549/354; 514/212; 514/228.2; 514/232.8; 514/253; 514/320; 514/374; 514/422; 540/596; 540/600; 544/62; 544/137; 544/147; 544/369; 544/375; 544/58.7; 546/196

[58] **Field of Search** 540/596, 602; 544/62, 544/137, 147, 369, 375, 98.7; 546/196; 548/215, 525; 549/354; 514/212, 222, 233, 234, 236, 237, 253, 320, 374, 422, 450, 228.2, 232.8

[56] **References Cited**

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3,354,155	11/1967	Tretter	549/354 X
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4,282,365	8/1981	Rokach	548/252
4,396,550	8/1983	Takizawa	549/354

US005116863A

[11] **Patent Number: 5,116,863**

[45] **Date of Patent: May 26, 1992**

4,465,835	8/1984	Takizawa	546/133
4,585,788	4/1986	Helsley et al.	549/354
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Chem. Abs., vol. 63 (1965) 16366a.
Drugs, vol. 13 (1977) 161:218.
J. Med. Chem., vol. 19, No. 7 (1976) 941:6.
J. Med. Chem., vol. 20, No. 11 (1977) 1499:501.
J. Med. Chem., vol. 21, No. 7 (1978) 633:9.

Primary Examiner—Richard L. Raymond
Attorney, Agent, or Firm—Fitzpatrick, Cella, Harper & Scinto

[57] **ABSTRACT**

Novel dibenz[b.e]oxepin derivatives are employed in the treatment and control of allergic conditions such as allergic asthma and also employed in the treatment of inflammation.

3 Claims, No Drawings

DIBENZ[B,E]OXEPIN DERIVATIVE AND PHARMACEUTICAL COMPOSITIONS THEREOF

BACKGROUND OF THE INVENTION

Heretofore, it has been known that 11-unsubstituted, 11-hydroxy or 11-oxodibenz[b,e]oxepin derivative is used for antiinflammatory agents [J. Med. Chem., 21, 633-639 (1978)]

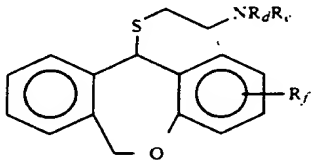
Further, it is known that dibenz[b,e]oxepin derivative wherein substitutents Ra and Rb at 11-position have the following definitions, is employed in the treatment and control of allergic conditions (U.S. Pat. No. 4,282,365).

Ra: H, OH, lower alkoxy, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, arylthio, NH_2, NHCHO or imidazolyl;

Rb: H or lower alkyl; or Ra and Rb taken together are =O, =CH—Rc wherein Rc is H or aryl.

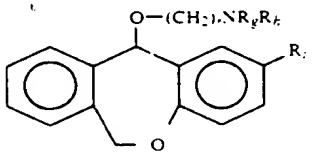
Furthermore, it is known that 11-(4-methylpiperazino) dibenz[b,e]oxepin derivative has an antiasthmatic activity (U.S. Pat. No. 4,396,550, U.S. Pat. No. 4,465,835, EP-A-38564).

It is also known that dibenz[b,e]oxepin derivative having the following formula:



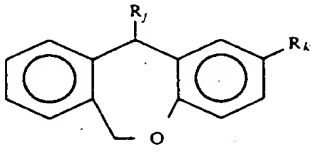
wherein Rd and Re are lower alkyl and Rf is lower alkyl or halogen, has an antiasthmatic activity (EP-A-85870).

Dibenz[b,e]oxepin derivative having an antiallergic activity and having the following structural formula:



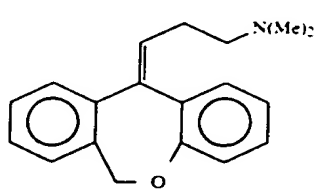
wherein Rg and Rh are alkyl, r is 2 or 3 and Ri is alkyl or halogen is known (JP-A-227879/84).

Dibenz[b,e]oxepin derivative having an antiallergic activity and having the following structural

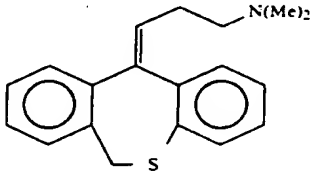


wherein Rj is 4-alkylpiperazino, 3-quinuclidylamino or —Xa—(CH_2)hd s—NR_lR_m wherein X_a is —NH—, —S— or —O—, s is 2 or 3 and R_l and R_m are alkyl, and R_k is CN, 5-tetrazolyl, $CONH_2$ or CO_2R_n wherein R_n is H, alkyl or 1-(ethoxycarbonyloxy)ethyl is known (EP-A-130555).

Doxepin having an antidepressant activity and having the following structural formula is known [Drugs. 13. 161 (1977)].



Dothiepin having an antidepressant activity and having the following structural formula is known [Arz.-Forsch., 13 1039 (1963); ibid., 14 100 (1964)].

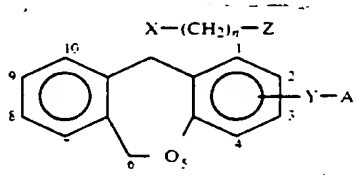


As the compound having both an antiallergic activity and an antiinflammatory activity, steroids are known.

It is always desired that a novel compound having an antiallergic activity or an antiinflammatory activity be developed.

SUMMARY OF THE INVENTION

The present invention relates to a dibenz[b,e]oxepin derivative represented by the formula (I):



(I)

Wherein A represents a hydroxymethyl, a lower alkoxymethyl, a triphenylmethyloxymethyl, a lower alkanoyloxymethyl, a lower alkanoyl, a carboxy, a lower alkoxy carbonyl, a triphenylmethyloxycarbonyl, —$CONR_1R_2$ (wherein R_1 and R_2 are the same or different and represent hydrogen atom or lower alkyl) 4,4-dimethyl-2-oxazoline-2-yl group or —CONHOH; Y represents —$(CH_2)_m$—, —CHR_3—(CH_2)m— or —CR_4=CR_5—(CH_2)hd m— which is substituent at 2— or 3-position of the mother nucleus (wherein R_3 represents a lower alkyl, R_4 and R_5 are the same or different and represent a hydrogen atom or a lower alkyl, m is 0, 1, 2, 3 or 4, and the left side of the group of Y mentioned above is bound to benzen nucleus); X represents =N—, =CH— or —CH_2—; n is 0, 1, 2, 3 or 4; Z represents 4-methylpiperazino, 4-methylhomopiperazino, piperidino, pyrrolidino, thiomorpholino, morpholino, or —NR_6R_7 (wherein R_6 and R_7 are the same or different and represent a hydrogen atom or a lower alkyl); and ⎓ means a single bond or double bond [hereinafter referred to as Compound (I) and Compounds with other formula numbers are hereinafter likewise referred to], and a pharmaceutically acceptable salt thereof. The present invention further pertains to a pharmaceutical

composition containing an effective amount of Compound (I) or a pharmaceutically acceptable salt thereof as an active ingredient, and a carrier or an excipient.

The present Compound (I) is useful for treatment of allergic conditions and inflammation.

DETAILED DESCRIPTION OF THE INVENTION

In the definition of each group of formula (I), the lower alkyl group includes straight or branched chain alkyl groups having 1 to 6 carbon atoms, for example, methyl, ethyl, n-propyl, iso-propyl, n-butyl, etc. In the definition of the group A, lower alkyl moiety of lower alkoxymethyl group and lower alkoxycarbonyl group has the same meaning as previously defined.

The lower alkoxymethyl group includes methoxymethyl, ethoxymethyl, n-propoxymethyl, isopropoxy, etc. and the lower alkoxycarbonyl group includes methoxycarbonyl, ethoxycarbonyl, etc.

In the definition of the group A, the lower alkyl moiety of lower alkanoyl group and lower alkanoyloxymethyl group has the same meaning as previously defined.

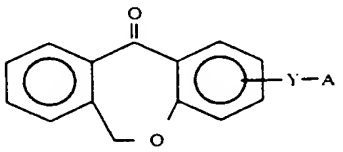
The lower alkanoyl group includes formyl, acetyl, etc. and the lower alkanoyloxymethyl group includes formyloxymethyl, acetyloxymethyl, etc.

The pharmaceutically acceptable salt of Compound (I) includes pharmaceutically acceptable acid addition salt, metal salt, ammonium salt, organic amine addition salt, amino acid addition salt, etc.

The pharmaceutically acceptable acid addition salt of Compound (I) includes inorganic acid salts such as hydrochloride, sulfate, phosphate, etc., and organic acid salts such as acetate, maleate, fumarate, tartrate, citrate, etc. The pharmaceutically acceptable metal salt includes alkalimetal salts such as sodium salt, potassium salt, etc., alkaline earch metal salts such as magnesium salt, calcium salt, etc., and alminium salt, zinc salt, etc. The pharmaceutically acceptable organic amine addition salt includes addition salt of morpholine and piperidine and the pharmaceutically acceptable amino acid addition salt includes addition salt of lysine, glysine, phenylalanine, etc.

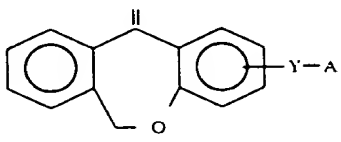
Compound (I) is prepared by using a compound represented by the formula (II):

(II)



wherein Y and A have the same meanings as previously defined or a compound represented by the formula (III):

(III)



wherein Y and A have the same meanings as previously defined as the starting compound. Compound (II) is

disclosed in J. Med. Chem., 19, 941 (1976), ibid., 20, 1499 (1977) and JP-A-21679/83.

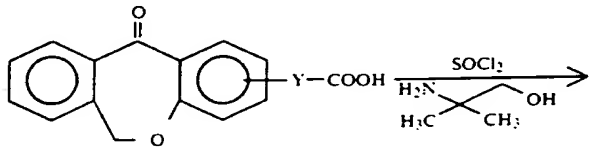
Compound (III) wherein —Y—A is —COOH is disclosed in JP-A-21679/83 and the other Compounds (III) can be prepared according to the method described in the publication though they do not occur in the publication.

The process for preparing Compound (I) is explained, depending on the kind of the group X.

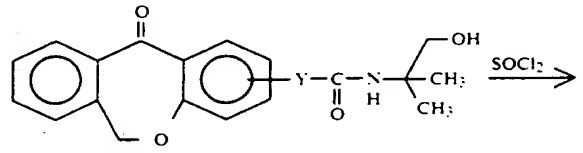
Process A

Synthesis of Compound (I) wherein X is =CH— (Part 1)

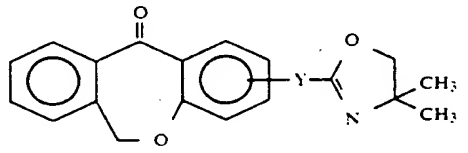
The carboxy group of Compound (IIa) is protected according to the following reaction scheme.



(IIa)



(IV)



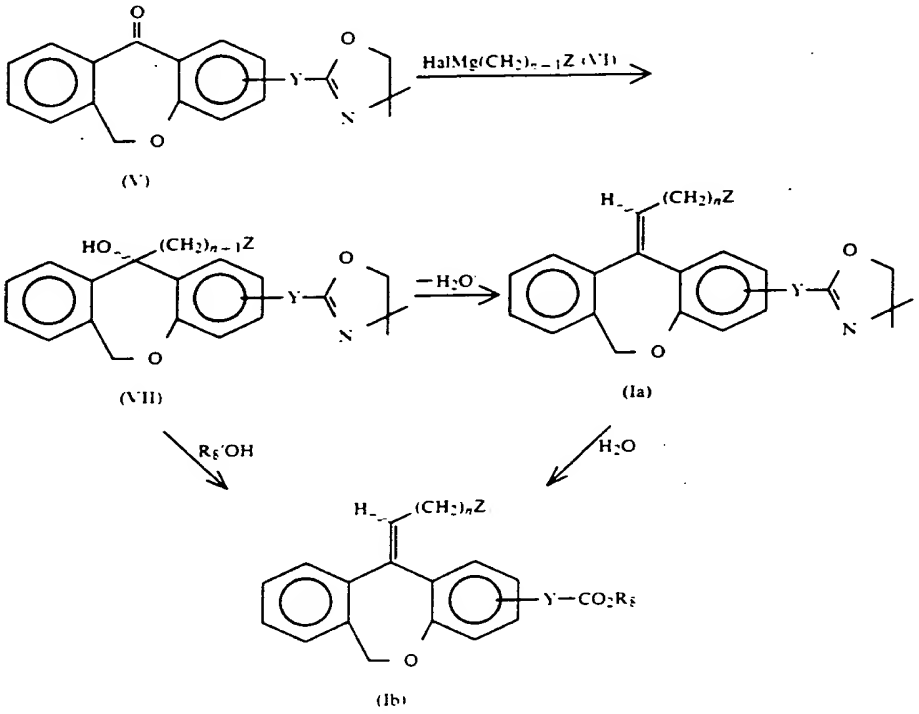
(V)

In the formulae, Y has the same meaning as previously defined, and Compound (IIa) is included in Compound (II) (compounds with an alphabet suffix following formula number are likewise included in compounds with common formula No.).

Compound (IIa) is reacted with 1 to 5 equivalents of thionyl chloride and 1 to 5 equivalents of 2-amino-2-methyl-1-propanol on the basis of Compound (IIa) in an inert solvent such as methylene chloride, if necessary in the presence of a base such as triethylamine at a temperature of from 0° C. to room temperature for 1–24 hours to form Compound (IV). Compound (IV) can also be obtained by reacting Compound (IIa) with thionyl chloride in advance and then with 2-amino-2-methyl-1-propanol.

Compound (IV) is reacted with 1–5 equivalents of thionyl chloride in an inert solvent such as methylene chloride, toluene and benzene at a temperature of from 0° C. to room temperature for 1–24 hours to form Compound (V).

Compounds (Ia) and (Ib) can be prepared from Compound (V) according to the following reaction scheme.



In the formulae. Y. Z. and n have the same meanings as previously defined. R_8 is hydrogen or a lower alkyl group. R'_8 is a lower alkyl group and Hal is halogen.

As used herein. the term lower alkyl has the same meaning as that of lower alkyl in each group of formula (I). Halogen includes chlorine. bromine and iodine. Compound (V) is reacted with 1-5 equivalents of Compound (VI) in an inert solvent such as tetrahydrofuran and diethyl ether under atmosphere of an inert gas such as nitrogen and argon to form Compound (VII). The reaction is carried out at a temperature of from 0° C. to room temperature and is usually completed in 1-24 hours.

Compound (VII) is reacted with 1-5 equivalents of thionyl chloride or phosphoryl chloride in an inert solvent such as methylene chloride in the presence of a base such as pyridine to form Compound (Ia). The reaction is carried out at a temperature of from 0° C. to room temperature and is completed in 1-24 hours.

Compound (Ia) is incubated in an alcohol containing water, such as aqueous methanol solution, in the pres-

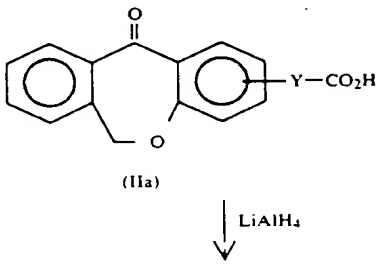
ence of an appropriate acidic catalyst such as p-toluenesulfonic acid at a temperature of from room temperature to the boiling point of the solvent to form Compound (Ib) wherein R_8 is H. The reaction is completed in 1-24 hours.

Compound (VII) is incubated in a alcohol of $R_8'OH$ in the presence of an appropriate acidic catalyst such as p-toluenesulfonic acid at a temperature of from room temperature to the boiling point of the solvent to form Compound (Ib) wherein R_8 is a lower alkyl. The reaction is completed in 1-24 hours.

Process B

Synthesis of Compound (I) wherein X is =CH— (Part 2)

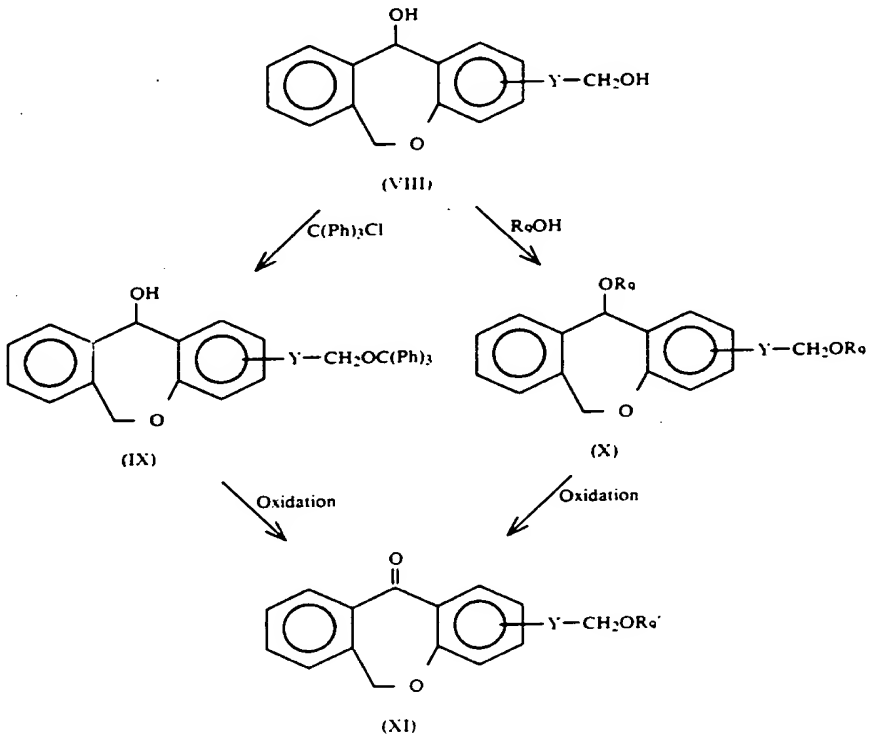
The carboxy group of a compound represented by the formula (IIa) can be converted to a lower alkoxymethyl group or a trityloxymethyl group according to the following reaction scheme.



(IIa)

↓ $LiAlH_4$

-continued

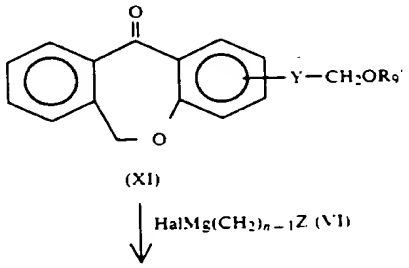


In the formulae, Y has the same meaning as previously defined, R_9 is a lower alkyl group and R_9' is a trityl group or a lower alkyl group. The term lower alkyl has the same meaning as that of lower alkyl in each group in formula (I).

Compound (IIa) is reduced with 1-5 equivalents of lithium aluminium hydride in tetrahydrofuran at a temperature of from 0° C. to room temperature for 1-24 hours to form Compound (VIII).

Compound (VIII) is reacted with 1-5 equivalents of trityl chloride in pyridine at a temperature of from room temperature to 100° C. for 1-24 hours to form Compound (IX).

Compound (IX) is oxidized with 1-5 equivalents of an appropriate oxidizing agent such as potassium permanganate and pyridinium chlorochromate in an inert solvent such as methylene chloride and acetone to form Compound (XI) wherein R_9' is trityl. The reaction is



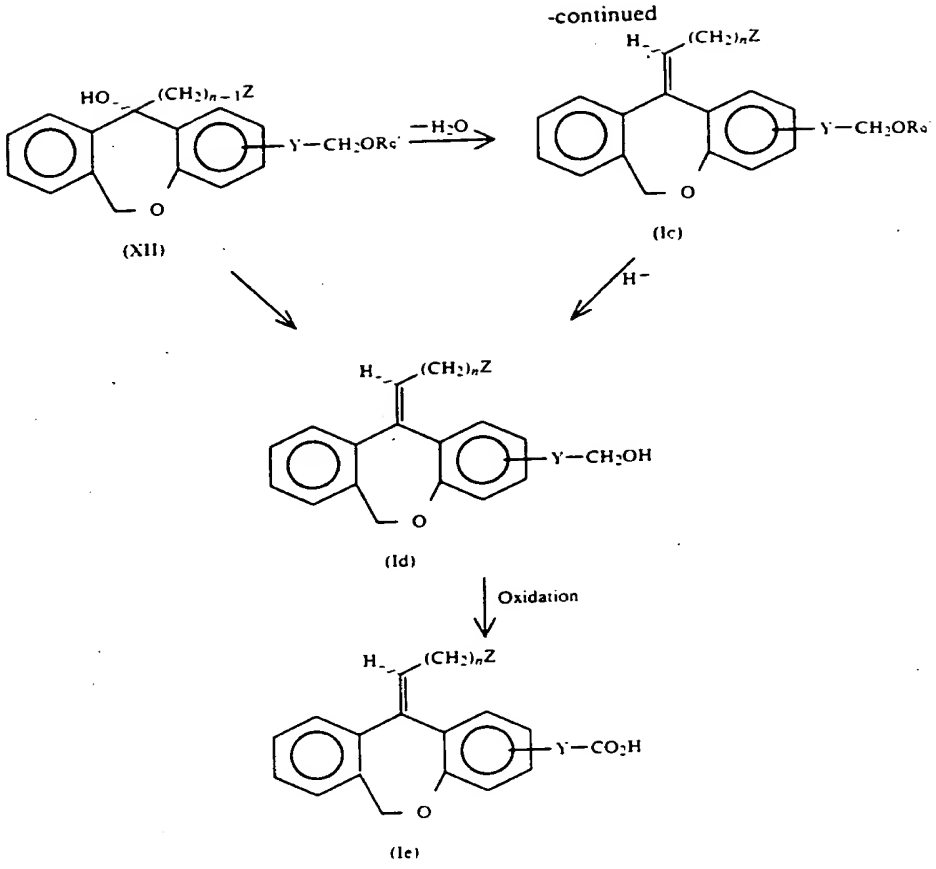
carried out at a temperature of from 0° C. to the boiling point of the solvent and is completed in 1–24 hours.

Compound (VIII) is incubated in an alcohol of R_9OH in the presence of an appropriate acidic catalyst such as sulfuric acid at a temperature of from room temperature to the boiling point of the solvent to form Compound (X). The reaction is usually completed in 1–24 hours.

Compound (X) is oxidized with 1–5 equivalents of an appropriate oxidizing agent such as Jones reagent in an inert solvent such as acetone to form Compound (XI) wherein R_9' is a lower alkyl. The reaction is carried out at a temperature of from 0° C. to the boiling point of the solvent and is usually completed in 1–24 hours.

The compounds represented by the formulae (Ic) and (Id) and if desired, the compound represented by the formula (Ie) can be synthesized from Compound (XI) according to the following reaction scheme.

-continued



In the formulae, Y, Z, R_o', n and Hal have the same meanings as previously defined.

Compound (XI) is reacted with Compound (VI) which is Grignard reagent according to the same manner as in the reaction step from Compound (V) to Compound (VII) in Process A to form Compound (XII).

Compound (XII) is subjected to reaction according to the same manner as in the reaction step from Compound (VII) to Compound (Ia) in Process A to form Compound (Ic).

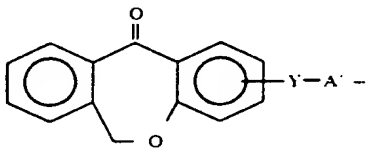
Compound (Ic) is incubated in a solvent containing water such as aqueous dioxane in the presence of an appropriate acidic catalyst such as p-toluenesulfonic acid at a temperature of from room temperature to the boiling point of the solvent to form Compound (Id). The reaction is usually completed in 1-24 hours.

Compound (Id) can also be obtained in one step by incubating Compound (XII) in a solvent containing water such as aqueous dioxane in the presence of an appropriate acidic catalyst such as sulfonic acid at a temperature of from room temperature to the boiling point of the solvent. The reaction is usually completed in 1-24 hours.

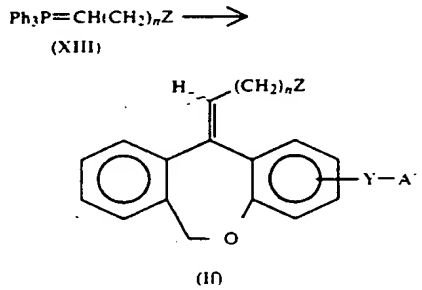
If desired, Compound (Id) is oxidized with 1-5 equivalents of an appropriate oxidizing agent such as Jones reagent in an inert solvent such as acetone to form Compound (Ie). The reaction is carried out at a temperature of from 0° C. to the boiling point of the solvent and is usually completed in 1-24 hours.

Process C

Synthesis of Compound (I) wherein X is =CH— (Part 3)



(IIb)



(I0)

In the formulae, Y, Z, and n have the same meanings as previously defined. A' represents the groups falling within the definition of A but lower alkanoyl group.

Compound (IIb) is reacted with 1-5 equivalents of Compound (XIII) in an inert solvent such as tetrahy-

drofuran under atmosphere of an inert gas such as nitrogen and argon at a temperature of from 0° C. to room temperature for 1-24 hours to form Compound (If).

Compound (XIII) which is ylide, can be prepared according to the method described in C.A. 63 16366a (1965).

$$Ph_3P - Hal(CH_2)_{n-1}Hal \longrightarrow$$
(XIV)

$$\overset{-}{Ph_3P}(CH_2)_{n-1}Hal.Hal^- \xrightarrow[2)\ HHal]{1)\ HZ}$$
(VX)

$$\overset{-}{Ph_3P}(CH_2)_{n+1}Z.Hal^-.(HHal)_q$$
(XVI)

In the formulae, Hal, n and Z have the same meanings as previously defined and q is 1 or 2.

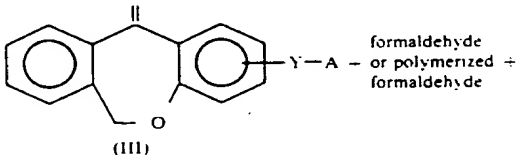
Compound (XIV) is reacted with an equivalent of triphenylphosphine in toluene at reflux of the solvent for 1-24 hours to form Compound (XV).

Compound (XV) is reacted with 1-5 equivalents of HZ in ethanol ar reflux of the solvent for 1-24 hours and excess HZ is distilled away under reduced pressure. After the addition of 1-5 equivalents of HHal on the basis of Compound (XV), the mixture is incubated at a temperature of from 0° C. to the boiling point of the solvent for 1-24 hours to form Compound (XVI) which is Wittig reagent.

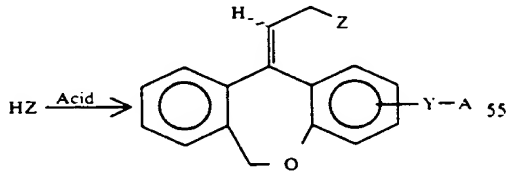
Compound (XVI) is treated with 1-2 equivalents of an appropriate base such as n-butyl lithium in an inert solvent such as tetrahydrofuran under atmosphere of an inert gas such as nitrogen and argon to form ylide (XIII). The reaction is carried out at −78° C. to room temperature and is usually completed in 1-24 hours.

Process D

Synthesis of Compound (I) wherein X is =CH— (Part 4)



(III)



(Ig)

In the formulae, Y, Z and A have the same meanings as previously defined.

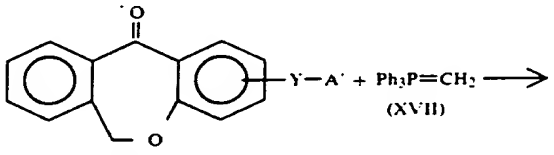
The process is known as Prince reaction [New Experimental Chemical Course (Maruzen), Vol. 14, Synthesis and Reaction of Organic Compound III, page 1375 (1977)].

Compound (III), 1 to 5 equivalents of formaldehyde and 1 to 5 equivalents of HZ are subjected to reaction in an inert solvent such as tetrachloroethane in the pres-

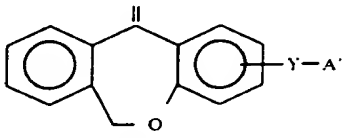
ence of an acid or reaction in an acid as such serving as a solvent under atmosphere of an inert gas such as nitrogen and argon to yield Compound (Ig).

The formaldehyde or polymerized formaldehyde includes p-formaldehyde, trioxane, etc. The acid includes acetic acid, trichloroacetic acid, trifluoroacetic acid, etc. The reaction is carried out at a temperature of from room temperature to the boiling point of the solvent and is completed in 1–24 hours.

Compound (III) which is the starting material can be prepared according to the process described in JP-A-21679/83, as shown below.



(IIb)



(IIIa)

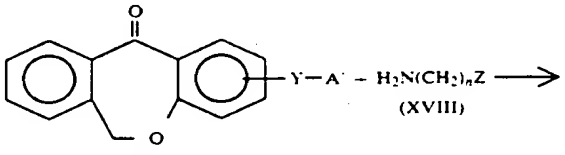
That is, Compound (IIb), 1 to 5 equivalents of methyltriphenylphosphonium bromide and 1 to 5 equivalents of n-butyl lithium on the basis of Compound (IIb) are subjected to reaction in an inert solvent at from −78° C. to room temperature for 1 to 5 hours to yield ylide (XVII) which is reacted with an equivalents of Compound (IIb) in an inert solvent at from −78° C. to room temperature under atmosphere of an inert gas for 1 to 24 hours to yield Compound (IIIa).

The inert gas includes nitrogen, argon, etc. and the inert solvent includes tetrahydrofuran, etc.

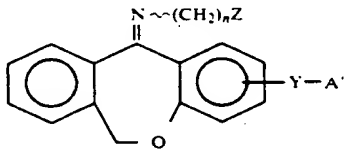
The group A' in Compound (IIIa) can easily be converted to a lower alkanoyl group as is stated in Process I and therefore, Compound (III) can easily be prepared.

Process E

Synthesis of Compound (I) wherein X is=N—



(IIb)



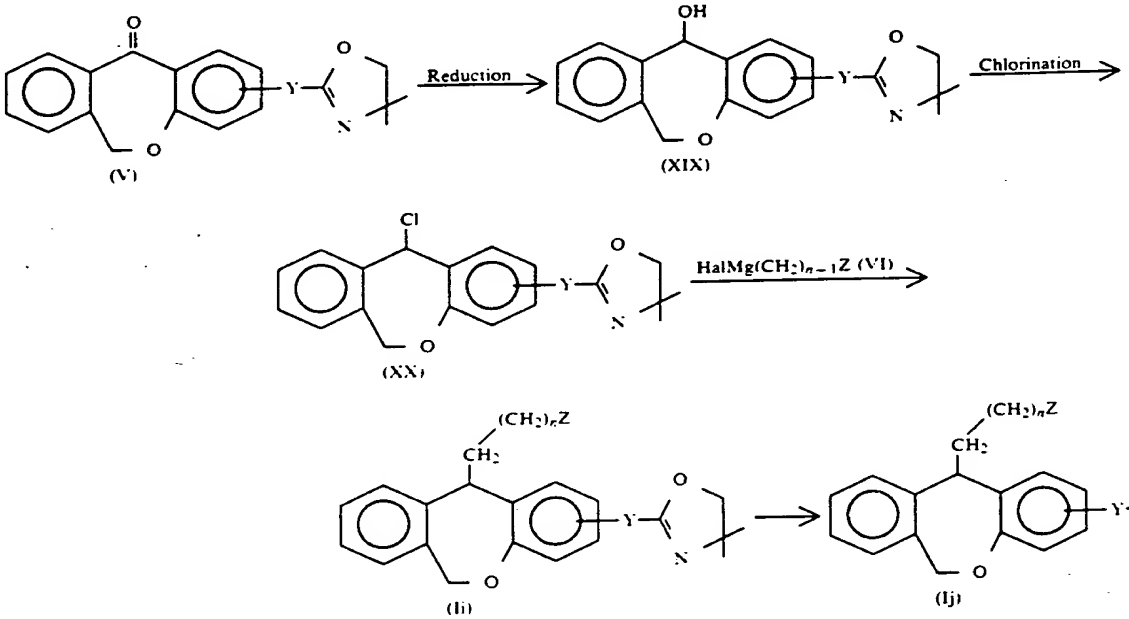
(Ih)

Compound (IIb) and 1 to 10 equivalents of Compound (XVIII) are subjected to reaction in an inert solvent such as benzene in the presence of 1 to 10 equivalents of titanium tetrachloride at from 0° C. to the

boiling point of the solvent under atmosphere of an inert gas such as nitrogen and argon for 1 to 48 hours to yield Compound (Ih).

Process F

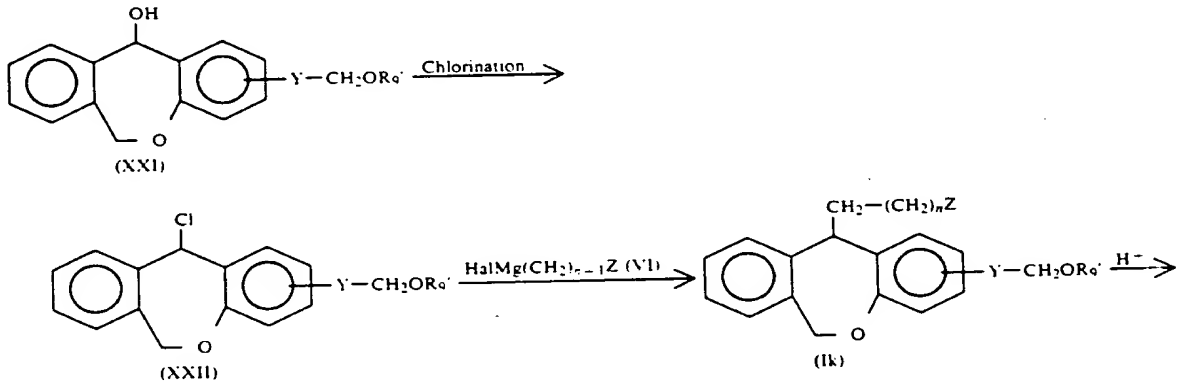
Synthesis of Compound (I) wherein X is $-CH_2-$ (Part 1)



In the formulae, Y, Z, n, R_8 and Hal have the same meanings as previously defined.

Compound (V) is reduced with 1 to 5 equivalent of lithium aluminium hydride or sodium borohydride in an inert solvent such as tetrahydrofuran and methanol at from 0° C. to room temperature for 1 to 24 hours to yield Compound (XIX).

Compound (XIX) and 1 to 5 equivalents of thionyl chloride or phosphoryl chloride are subjected to reac-



tion in an appropriate base such as pyridine at from 0° C. to room temperature to yield Compound (XX).

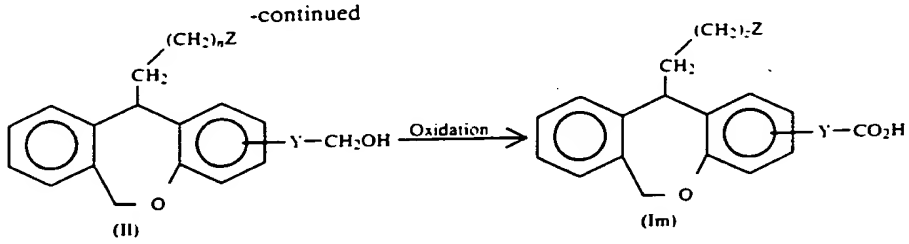
Compound (XX) and 1 to 5 equivalents of Compound (VI) are subjected to reaction in the same manner as in the reaction step from Compound (V) to Compound (VII) in Process A to yield Compound (Ii).

Compound (Ii) is subjected to reaction in the same manner as in the reaction step from Compound (VII) to Compound (Ib) or the reaction step from Compound (Ia) to Compound (Ib) in Process A to yield Compound (Ij).

Process G

Synthesis of Compound (I) wherein X is $-CH_2-$ (Part 2)

-continued



(II) (Im)

Compound (XXI) is subjected to chlorination in the same manner as in Process F to yield Compound (XXII). Compound (XXII) and Compound (VI) are subjected to reaction in the same manner as in Process F to yield Compound (Ik). Compound (Ik) is treated in the same manner as in Process B to form Compound (Il).

Compound (Il) is further treated to form Compound (Im).

Compound (IX) is included in the definition of the starting material (XXI).

Compound (XI) is reduced with 1 to 5 equivalents of lithium alminium hydride or sodium borohydride in an inert solvent such as tetrahydrofuran and methanol at from 0° C. to room temperature for 1 to 24 hours to yield Compound (XXI).

Process H

Synthesis of Compound (I) wherein X is —CH_2— (Part 3)

Compound (I) wherein X is —CH_2— can also be prepared by subjecting Compounds (Ia)-(Ig) obtained by the Processes A-D to reduction such as hydrogenation using paradium-carbon as catalyst.

The intermediates and the desired compounds in each of the processes described above can be purified and isolated by a purification method which is usually used in the field of organic chemical synthesis, such as filtration, extraction with organic solvent such as ethyl acetate and methylene chloride, drying, concentration, recrystallization, column chromatography, etc.

Out of Compounds (Ia)-(Ih) obtained in each of the processes described above, with regard to stereochemistry at 11-position of dibenz[b,e]oxepin, Compounds (Ia), (Ib), (Ic), (Id), (Ig) and (Ih) are apt to be formed as a trans-form and Compound (If) is apt to be formed as a cis-form, with high frequency compared with the other form.

When Compound (I) except Compounds (Ii)-(Im) is produced as a cis-trans mixture, Compound (I) is separated and purified by an appropriate method which is usually used in the field of organic chemical synthesis, such as column chromatography, recrystallization, etc.

If desired, cis-form can be converted to trans-form. For example, cis-form is added to an acetic acid and the mixture is heated at reflux in the presence of an appropriate catalyst such as p-toluenesulfonic acid for 1-24 hours to form trans-form.

With regard to the denotation of cis-form (or cin-form) and trans form (or anti-form) of Compound (I), Compound (I) wherein the substituent bound to the double bond is on the same side as oxygen of oxepin, is cis-form (or cin-form) and Compound (I) wherein the substituent is on the opposite side is trans-form (or anti-form).

Further, if cis- or trans-form is denoted according to E-Z expression, cis-form (or cin-form) is Z-form and trans-form (or anti-form) is E-form.

For example, the compound represented by the following formula is cis-form (or cin-form or Z-form).

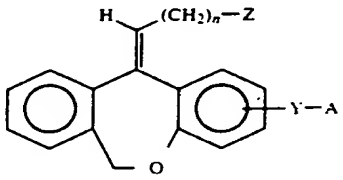


Table 1 shows examples of Compound (I) or pharmaceutically acceptable salts thereof and Table 2 shows the structural formula thereof.

Table 3 shows characteristic signals in NMR and Table 4 shows retention time in HPLC.

TABLE 1

Compound No.	Compound (I)
1	Methyl cis-11-(3-dimethylaminopropylidene)-6.11-dihydrodibenz[b.e]oxepin-2-carboxylate Methyl trans-11-(3-dimethylaminopropylidene)-6.11-dihydrodibenz[b.e]oxepin-2-carboxylate
2	Ethyl cis-11-(3-dimethylaminopropylidene)-6.11-dihydrodibenz[b.e]oxepin-2-carboxylate Ethyl trans-11-(3-dimethylaminopropylidene)-6.11-dihydrodibenz[b.e]oxepin-2-carboxylate
3	Cis-11-(3-dimethylaminopropylidene)-6.11-dihydrodibenz[b.e]oxepin-2-carboxylic acid Trans-11-(3-dimethylaminopropylidene)-6.11-dihydrodibenz[b.e]oxepin-2-carboxylic acid
4	Methyl cis-11-(3-diethylaminopropylidene)-6.11-dihydrodibenz[b.e]oxepin-2-carboxylate Methyl trans-11-(3-diethylaminopropylidene)-6.11-dihydrodibenz[b.e]oxepin-2-carboxylate
5	Cis-11-(3-diethylaminopropylidene)-6.11-dihydrodibenz[b.e]oxepin-2-carboxylic acid Trans-11-(3-diethylaminopropylidene)-6.11-dihydrodibenz[b.e]oxepin-2-carboxylic acid
6	Methyl cis-11-(3-pyrrolidinepropylidene)-6.11-dihydrodibenz[b.e]oxepin-2-carboxylate Methyl trans-11-(3-pyrrolidinopropylidene)-6.11-dihydrodibenz[b.e]oxepin-2-carboxylate
7	Cis-11-(3-pyrrolidinopropylidene)-6.11-dihydrodibenz[b.e]oxepin-2-carboxylic acid Trans-11-(3-pyrrolidinopropylidene)-6.11-dihydrodibenz[b.e]oxepin-2-carboxylic acid
8	Methyl cis-11-(4-dimethylaminobutylidene)-6.11-dihydrodibenz[b.e]oxepin-2-carboxylate Methyl trans-11-(4-dimethylaminobutylidene)-6.11-dihydrodibenz[b.e]oxepin-2-carboxylate
9	Cis-11-(4-dimethylaminobutylidene)-6.11-dihydrodibenz[b.e]oxepin-2-carboxylic acid Trans-11-(4-dimethylaminobutylidene)-6.11-dihydrodibenz[b.e]oxepin-2-carboxylic acid
10	Methyl cis-11-[2-(4-methylpiperazino)-ethylidene]-6.11-dihydrodibenz[b.e]oxepin-2-carboxylate Methyl trans-11-[2-(4-methylpiperazino)-ethylidene]-6.11-dihydrodibenz[b.e]oxepin-2-carboxylate

TABLE 1-continued

Compound No.	Compound (I)
11	Cis-11-[2-(4-methylpiperazino)ethylidene]-6.11-dihydrodibenz[b.e]oxepin-2-carboxylic acid Trans-11-[2-(4-methylpiperazino)ethylidene]-6.11-dihydrodibenz[b.e]oxepin-2-carboxylic acid
12	Methyl cis-11-(2-morpholinoethylidene)-6.11-dihydrodibenz[b.e]oxepin-2-carboxylate Methyl trans-11-(2-morpholinoethylidene)-6.11-dihydrodibenz[b.e]oxepin-2-carboxylate
13	Cis-11-(2-morpholinoethylidene)-6.11-dihydrodibenz[b.e]oxepin-2-carboxylic acid Trans-11-(2-morpholinoethylidene)-6.11-dihydrodibenz[b.e]oxepin-2-carboxylic acid
14	Methyl cis-11-(2-thiomorpholinoethylidene)-6.11-dihydrodibenz[b.e]oxepin-2-carboxylate Methyl trans-11-(2-thiomorpholinoethylidene)-6.11-dihydrodibenz[b.e]oxepin-2-carboxylate
15	Cis-11-(2-thiomorpholinoethylidene)-6.11-dihydrodibenz[b.e]oxepin-2-carboxylic acid Trans-11-(2-thiomorpholinoethylidene)-6.11-dihydrodibenz[b.e]oxepin-2-carboxylic acid
16	Methyl cis-11-(2-pyrrolidinoethylidene)-6.11-dihydrodibenz[b.e]oxepin-2-carboxylate Methyl trans-11-(2-pyrrolidinoethylidene)-6.11-dihydrodibenz[b.e]oxepin-2-carboxylate
17	Methyl cis-11-(2-piperidinoethylidene)-6.11-dihydrodibenz[b.e]oxepin-2-carboxylate Methyl trans-11-(2-piperidinoethylidene)-6.11-dihydrodibenz[b.e]oxepin-2-carboxylate
18	Methyl cis-11-(3-dimethylaminopropylidene)-6.11-dihydrodibenz[b.e]oxepin-2-acetate Methyl trans-11-(3-dimethylaminopropylidene)-6.11-dihydrodibenz[b.e]oxepin-2-acetate
19	Ethyl cis-11-(3-dimethylaminopropylidene)-6.11-dihydrodibenz[b.e]oxepin-2-acetate Ethyl trans-11-(3-dimethylaminopropylidene)-6.11-dihydrodibenz[b.e]oxepin-2-acetate
20	Cis-11-(3-dimethylaminopropylidene)-6.11-dihydrodibenz[b.e]oxepin-2-acetic acid Trans-11-(3-dimethylaminopropylidene)-6.11-dihydrodibenz[b.e]oxepin-2-acetic acid
21	Methyl cis-11-(4-dimethylaminobutylidene)-6.11-dihydrodibenz[b.e]oxepin-2-acetate Methyl trans-11-(4-dimethylaminobutylidene)-6.11-dihydrodibenz[b.e]oxepin-2-acetate
22	Cis-11-(4-dimethylaminobutylidene)-6.11-dihydrodibenz[b.e]oxepin-2-acetic acid Trans-11-(4-dimethylaminobutylidene)-6.11-dihydrodibenz[b.e]oxepin-2-acetic acid
23	Methyl cis-11-(3-pyrrolidinopropylidene)-6.11-dihydrodibenz[b.e]oxepin-2-acetate Methyl trans-11-(3-pyrrolidinopropylidene)-6.11-dihydrodibenz[b.e]oxepin-2-acetate
24	Cis-11-(3-pyrrolidinopropylidene)-6.11-dihydrodibenz[b.e]oxepin-2-acetic acid Trans-11-(3-pyrrolidinopropylidene)-6.11-dihydrodibenz[b.e]oxepin-2-acetic acid
25	Methyl cis-11-[2-(4-methylpiperazino)-ethylidene-6.11-dihydrodibenz[b.e]oxepin-2-acetate Methyl trans-11-[2-(4-methylpiperazino)-ethylidene)-6.11-dihydrodibenz[b.e]oxepin-2-acetate
26	Cis-11-[2-(4-methylpiperazino)-ethylidene-6.11-dihydrodibenz[b.e]oxepin-2-acetic acid Trans-11-[2-(4-methylpiperazino)-ethylidene)-6.11-dihydrodibenz[b.e]oxepin-2-acetic acid
27	Methyl cis-3-[11-(3-dimethylaminopropylidene)-6.11-dihydrodibenz[b.e]oxepin-2-yl]-propionate Methyl trans-3-[11-(3-dimethylaminopropylidene)-6.11-dihydrodibenz[b.e]oxepin-2-yl]-propionate
28	Cis-3-[11-(3-dimethylaminopropylidene)-6.11-dihydrodibenz[b.e]oxepin-2-yl]-propionic acid Trans-3-[11-(3-dimethylaminopropylidene)-6.11-dihydrodibenz[b.e]oxepin-2-yl]-propionic acid
29	Methyl cis-11-(3-dimethylaminopropylidene)-6.11-dihydrodibenz[b.e]oxepin-3-acetate Methyl trans-11-(3-dimethylaminopropylidene)-6.11-dihydrodibenz[b.e]oxepin-3-acetate
30	Cis-11-(3-dimethylaminopropylidene)-6.11-

TABLE 1-continued

Compound No.	Compound (I)
	dihydrodibenz[b.e]oxepin-3-acetic acid
	Trans-11-(3-dimethylaminopropylidene)-6.11-dihydrodibenz[b.e]oxepin-3-acetic acid
31	Cis-11-(3-dimethylaminopropylidene)-2-(2-hydroxyethyl)-6.11-dihydrodibenz[b.e]oxepin
	Trans-11-(3-dimethylaminopropylidene)-2-(2-hydroxyethyl)-6.11-dihydrodibenz[b.e]oxepin
32	Cis-11-(3-dimethylaminopropylidene)-2-(2-triphenylmethyloxymethyl)-6.11-dihydrodibenz-[b.e]oxepin
	Trans-11-(3-dimethylaminopropylidene)-2-(2-triphenylmethyloxymethyl)-6.11-dihydrodibenz-[b.e]oxepin
33	Cis-11-(3-dimethylaminopropylidene)-2-(3-hydroxypropyl)-6.11-dihydrodibenz[b.e]oxepin
	Trans-11-(3-dimethylaminopropylidene)-2-(3-hydroxypropyl)-6.11-dihydrodibenz[b.e]oxepin
34	Methyl cin-11-(2-diethylaminoethyl)imino-6.11-dihydrodibenz[b.e]oxepin-2-carboxylate
	Methyl anti-11-(2-diethylaminoethyl)imino-6.11-dihydrodibenz[b.e]oxepin-2-carboxylate
35	Cin-11-(2-diethylaminoethyl)imino-6.11-dihydrodibenz[b.e]oxepin-2-carboxylic acid
	Anti-11-(2-diethylaminoethyl)imino-6.11-dihydrodibenz[b.e]oxepin-2-carboxylic acid
36	Methyl cin-11-(2-dimethylaminoethyl)imino-6.11-dihydrodibenz[b.e]oxepin-2-acetate
	Methyl anti-11-(2-dimethylaminoethyl)imino-6.11-dihydrodibenz[b.e]oxepin-2-acetate
37	Cin-11-(2-dimethylaminoethyl)imino-6.11-dihydrodibenz[b.e]oxepin-2-acetic acid
	Anti-11-(2-dimethylaminoethyl)imino-6.11-dihydrodibenz[b.e]oxepin-2-acetic acid
38	Methyl cin-11-(2-diethylaminoethyl)imino-6.11-dihydrodibenz[b.e]oxepin-2-acetate
	Methyl anti-11-(2-diethylaminoethyl)imino-6.11-dihydrodibenz[b.e]oxepin-2-acetate
39	Cin-11-(2-diethylaminoethyl)imino-6.11-dihydrodibenz[b.e]oxepin-2-acetic acid
	Anti-11-(2-diethylaminoethyl)imino-6.11-dihydrodibenz[b.e]oxepin-2-acetic acid
40	Methyl cin-11-(3-dimethylaminopropyl)imino-6.11-dihydrodibenz[b.e]oxepin-2-acetate
	Methyl anti-11-(3-dimethylaminopropyl)imino-6.11-dihydrodibenz[b.e]oxepin-2-acetate
41	Cin-11-(3-dimethylaminopropyl)imino-6.11-dihydrodibenz[b.e]oxepin-2-acetic acid
	Anti-11-(3-dimethylaminopropyl)imino-6.11-dihydrodibenz[b.e]oxepin-2-acetic acid
42	Methyl cin-3-[11-(2-diethylaminoethyl)imino-6.11-dihydrodibenz[b.e]oxepin-2-yl]-propionate
	Methyl anti-3-[11-(2-diethylaminoethyl)imino-6.11-dihydrodibenz[b.e]oxepin-2-yl]-propionate
43	Cin-[11-(2-diethylaminoethyl)imino-6.11-dihydrodibenz[b.e]oxepin-2-yl]-propionic acid
	Anti-[11-(2-diethylaminoethyl)imino-6.11-dihydrodibenz[b.e]oxepin-2-yl]-propionic acid
44	Methyl cin-2-[11-(2-dimethylaminoethyl)imino-6.11-dihydrodibenz[b.e]oxepin-2-yl]-propionate
	Methyl anti-2-[11-(2-dimethylaminoethyl)imino-6.11-dihydrodibenz[b.e]oxepin-2-yl]-propionate
45	Cin-2-[11-(2-dimethylaminoethyl)imino-6,11-dihydrodibenz[b.e]oxepin-2-yl]-propionic acid
	Anti-2-[11-(2-dimethylaminoethyl)imino-6.11-dihydrodibenz[b.e]oxepin-2-yl]-propionic acid
46	Methyl cin-11-(2-dimethylaminoethyl)imino-6.11-dihydrodibenz[b.e]oxepin-3-acetate
	Methyl anti-11-(2-dimethylaminoethyl)imino-6.11-dihydrodibenz[b.e]oxepin-3-acetate
47	Cin-11-(2-dimethylaminoethyl)imino-6.11-dihydrodibenz[b.e]oxepin-3-acetic acid
	Anti-11-(2-dimethylaminoethyl)imino-6.11-dihydrodibenz[b.e]oxepin-3-acetic acid
48	Methyl cin-11-(3-dimethylaminopropyl)imino-6.11-dihydrodibenz[b.e]oxepin-3-acetate
	Methyl anti-11-(3-dimethylaminopropyl)imino-6.11-dihydrodibenz[b.e]oxepin-3-acetate
49	Cin-11-(3-dimethylaminopropyl)imino-6.11-dihydrodibenz[b.e]oxepin-3-acetic acid
	Anti-11-(3-dimethylaminopropyl)imino-6.11-

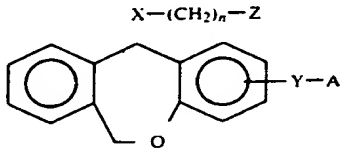
TABLE 1-continued

Compound No.	Compound (I)
	dihydrodibenz[b.e]oxepin-3-acetic acid
50	Methyl 11-(3-dimethylaminopropyl)-6.11-dihydrodibenz[b.e]oxepin-2-carboxylate
51	11-(3-dimethylaminopropyl)-6.11-dihydrodibenz-[b.e]oxepin-2-carboxylic acid
52	11-(3-dimethylaminopropyl)-6.11-dihydrodibenz-[b.e]oxepin-2-acetic acid
53	11-(3-Dimethylaminopropylidene)-2-(4.4-dimethyl-2-oxazoline-2-yl)-6.11-dihydrodibenz-[b.e]oxepin
54	11-(3-Dimethylaminopropyl)-2-(4.4-dimethyl-2-oxazoline-2-yl)-6.11-dihydrodibenz[b.e]oxepin
55	Methyl cis-11-(3-morpholinopropylidene)-6.11-dihydrodibenz[b.e]oxepin-2-carboxylate
	Methyl trans-11-(3-morpholinopropylidene)-6.11-dihydrodibenz[b.e]oxepin-2-carboxylate
56	Cis-11-(3-morpholinopropylidene)-6.11-dihydro-dibenz[b.e]oxepin-2-carboxylic acid
	Trans-11-(3-morpholinopropylidene)-6.11-dihydrodibenz[b.e]oxepin-2-carboxylic acid
57	Methyl cis-11-(3-thiomorpholinopropylidene)-6.11-dihydrodibenz[b.e]oxepin-2-carboxylate
	Methyl trans-11-(3-thiomorpholinopropylidene)-6.11-dihydrodibenz[b.e]oxepin-2-carboxylate
58	Cis-11-(3-thiomorpholinopropylidene)-6.11-dihydrodibenz[b.e]oxepin-2-carboxylic acid
	Trans-11-(3-thiomorpholinopropylidene)-6.11-dihydrodibenz[b.e]oxepin-2-carboxylic acid
59	Methyl trans-3-[cis-11-(3-dimethylaminopro-pylidene)-6.11-dihydrodibenz[b.e]oxepin-2-yl]-acrylate
	Methyl trans-3-[trans-11-(3-dimethylaminopro-pylidene)-6.11-dihydrodibenz[b.e]oxepin-2-yl]-acrylate
60	Trans-3-[cis-11-(3-dimethylaminopropylidene)-6.11-dihydrodibenz[b.e]oxepin-2-yl]-acrylic acid
	Trans-3-[trans-11-(3-dimethylaminopropylidene)-6.11-dihydrodibenz[b.e]oxepin-2-yl]-acrylic acid
61	Methyl cis-11-(3-methylaminopropylidene)-6.11-dihydrodibenz[b.e]oxepin-2-acetate
	Methyl trans-11-(3-methylaminopropylidene)-6.11-dihydrodibenz[b.e]oxepin-2-acetate
62	Cis-11-(3-methylaminopropylidene)-6.11-dihydrodibenz[b.e]oxepin-2-acetic acid
	Trans-11-(3-methylaminopropylidene)-6.11-dihydrodibenz[b.e]oxepin-2-acetic acid
63	Methyl cis-11-(3-aminopropylidene)-6.11-dihydrodibenz[b.e]oxepin-2-acetate
	Methyl trans-11-(3-aminopropylidene)-6.11-dihydrodibenz[b.e]oxepin-2-acetate
64	Cis-11-(3-aminopropylidene)-6.11-dihydrodibenz-[b.e]oxepin-2-acetic acid
	Methyl trans-11-(3-aminopropylidene)-6.11-dihydrodibenz[b.e]oxepin-2-acetic acid
3'	½ Fumarate · 1/5 hydrate of Compound 3 (trans form 99%)
5'	Fumarate · ½ hydrate of Compound 5 (cis form 99%)
7'	Fumarate · 1 hydrate of Compound 7 (cis form 70%)
11'	2 Fumarate · ½ hydrate of Compound 11 (trans form 100%)
13'	½ Fumarate · ½ hydrate of Compound 13 (trans form 93%)
15'	Fumarate of Compound 15 (trans form 100%)
20'	Fumarate · 3/2 hydrate of Compound 20 (trans form 95%)
26'	Fumarate · ⅓ hydrate of Compound 26 (trans form 88%)
28'	Fumarate · ½ hydrate of Compound 28 (trans form 63%)
31'	½ Fumarate · 1 hydrate of Compound 31 (trans form 95%)
33'	Fumarate of Compound 33 (cis form 100%)
35'	Sodium salt · 1 hydrate of Compound 35 (anti:cin = 1:1)

TABLE 1-continued

Compound No.	Compound (I)
43	Sodium salt of Compound 43 (anti form 98%)
45	Sodium salt · 1 hydrate of Compound 45 (anti form 99%)
60	Fumarate of Compound 60 (cis form 100%)

TABLE 2



Me: methyl group
Ph: pheny group
Et: ethyl group

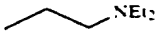
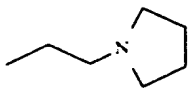
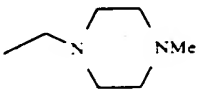
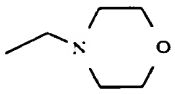
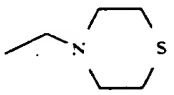
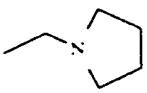
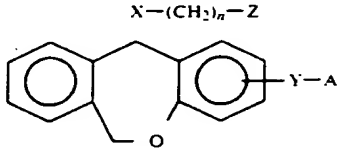
Compound No.	X	—Y—A	—(CH2)n—Z
1	CH	2-COOMe	
2	"	2-COOEt	"
3	"	2-COOH	"
4	"	2-COOMe	
5	"	2-COOH	"
6	"	2-COOMe	
7	"	2-COOH	"
8	"	2-COOMe	
9	"	2-COOH	"
10	"	2-COOMe	
11	"	2-COOH	"
12	"	2-COOMe	
13	"	2-COOH	"
14	"	2-COOMe	
15	"	2-COOH	"
16	"	2-COOMe	

TABLE 2-continued



Me: methyl group
Ph: pheny group
Et: ethyl group

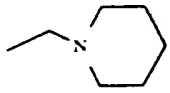
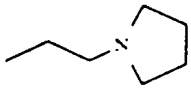
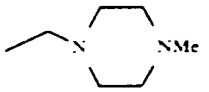
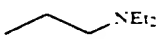
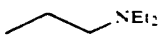
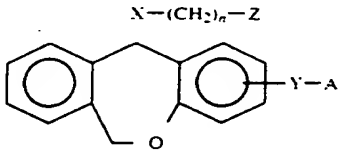
Compound No.	X	—Y—A	—(CH2)n—Z
17	"	2-COOMe	
18	CH	2-CH_2COOMe	
19	"	2-CH_2COOEt	"
20	"	2-CH_2COOH	"
21	"	2-CH_2COOMe	
22	"	2-CH_2COOH	"
23	"	2-CH_2COOMe	
24	"	2-CH_2COOH	"
25	"	2-CH_2COOMe	
26	"	2-CH_2COOH	"
27	"	2-CH_2CH_2COOMe	
28	"	2-CH_2CH_2COOH	"
29	"	3-CH_2COOMe	"
30	"	3-CH_2COOH	"
31	"	2-CH_2CH_2OH	"
32	"	2-$CH_2CH_2OC(Ph)_3$	"
33	"	2-$CH_2CH_2CH_2$OH	"
34	N	2-COOMe	
35	"	2-COOH	"
36	"	2-CH_2COOMe	
37	"	2-CH_2COOH	"
38	N	2-CH_2COOMe	
39	"	2-CH_2COOH	"
40	"	2-CH_2COOMe	
41	"	2-CH_2COOH	"
42	"	2-CH_2CH_2COOMe	
43	"	2-CH_2CH_2COOH	"
44	"	2-$CH(CH_3)$COOMe	

TABLE 2-continued



Me: methyl group
Ph: pheny group
Et: ethyl group

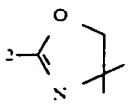
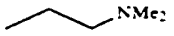
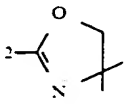
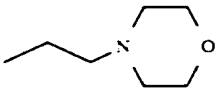
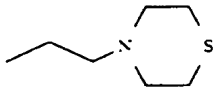
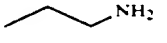
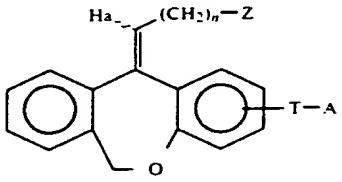
Compound No.	X	—Y—A	—(CH2)n—Z
45	"	2-CH(CH3)COOH	"
46	"	3-CH2COOMe	"
47	"	3-CH2COOH	"
48	"	3-CH2COOMe	
49	"	3-CH2COOH	"
50	CH2	2-COOMe	
51	"	2-COOH	"
52	"	2-CH2COOH	"
53	CH		
54	CH2		"
55	CH	2-COOMe	
56	"	2-COOH	"
57	CH	2-COOMe	
58	"	2-COOH	"
59	"	2-CH=CH—COOMe	
60	"	2-CH=CH—COOH	"
61	"	2-CH2COOMe	
62	"	2-CH2COOH	"
63	"	2-CH2COOMe	
64	"	2-CH2COOH	"

TABLE 3



Compound	Chemical sift of Ha proton (ppm) Cis	Trans	Measure solvent
1	5.67	6.06	A
2	5.70	6.07	A
3	5.72	6.09	B
4	5.69	6.05	A
5	5.73	—	B
6	5.70	6.07	A
7	5.71	6.09	B
8	5.70	6.08	A
9	5.71	6.08	B
10	5.85	6.22	A
11	—	6.11	B
12	5.81	6.20	A
13	5.81	6.13	B
14	5.81	6.18	A
15	5.80	6.13	B
16	5.83	6.19	A
17	5.92	6.28	A
18	5.69	6.06	A
19	5.70	6.07	B
20	5.66	6.00	B
21	5.66	6.02	B
22	5.67	6.02	B
23	5.69	5.99	A
24	5.60	5.92	A
25	5.84	6.17	A
26	5.72	6.05	B
27	5.69	6.57	A
28	5.50	5.99	B
31	5.66	5.99	A
32	5.69	6.97	A
33	5.65		A
55	5.67	6.06	A
56	5.73	6.10	B
57	5.68	6.03	A
58	5.70	6.08	B
59	5.72	—	A
60	5.71	—	B
61	5.63	—	A
62	5.65	—	B
63	5.68	—	A
64	5.67	—	B

A = $CDCl_3$
B = DMSO-d_6

TABLE 4

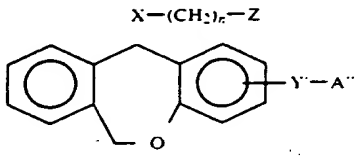
Compound	Retention time in HPLC (Minutes) Cis	Trans	Eluent
3	10.33	8.33	B
5	7.19	6.06	C
7	10.83	8.79	B
9	14.26	11.40	B
11	27.06	21.33	A
13	16.59	13.13	A
15	—	14.73	A
20	9.93	7.46	B
22	11.10	8.40	B
24	10.50	8.00	B
26	11.20	8.93	B
28	11.60	9.10	B
33	11.06	—	B
56	11.34	8.95	B
58	12.41	7.75	B
60	11.29	—	B
62	10.77	—	B

TABLE 4-continued

Compound	Retention time in HPLC (Minutes) Cis	Trans	Eluent
64	10.65	—	B

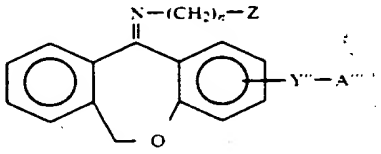
Instrument:	SHIMAZU LC-3A
Column	Yamamurakagaku YMC A-312
	A 0.01M PIC B-8
	in 54.3% MeOH
	B 0.01M PIC B-8
	in 61.3% MeOH
	C 0.01M PIC B-8
	in 66.0% MeOH
* PIC:	PIC reagent (Produced by Water Associates)
Pressure:	85–95 kg/cm^2
Temperature:	room temperature

Compound (I) has both an antiallergic activity and antiinflammatory activity. Among Compound (I), the compound represented by the formula (I') has strong antiallergic activity and the compound represented by the formula (II') has strong antiinflammatory activity.



(I')

In the formula, X, n and Z are as previously defined, —Y''—A'' is —Y—A when X is =CH— or —CH$_2$— and is —Y—A which is bound at 2 position of the mother nucleus when X is =N—, and Y and A are as previously defined.



(II')

In the formula, n and Z are as previously defined; Y''' is —CH$_2$— or —CHR$_3$— substituted at 2 or 3 position of the mother nucleus wherein R$_3$ is a lower alkyl; A''' is a hydroxymethyl, a loweralkoxymethyl, a triphenylmethyloxymethyl, a lower alkanoyloxymethyl, a formyl, a carboxyl, a lower alkoxycarbonyl, a triphenylmethyloxycarbonyl, —CONR$_1$R$_2$ wherein R$_1$ and R$_2$ are the same or different and are hydrogen atom or a lower alkyl, 4,4-dimethyl-2-oxazoline-2-yl or —CONHOH.

The antiallergic activity and antiinflammatory activity of Compound (I) are described below:

Test for antiallergic activity

Antiallergic activity was investigated by a homologous PCA (passive cutaneous anaphlaxis) of rats for 48 hours, where Wistar male rats having body weights of 180 to 220 g were used for sampling of antiserum and Wistar male rats having body weights of 120 to 140 g were used for the PCA test.

A) Preparation of anti EWA rat serum

Anti-egg white albumin (EWA) rat serum was prepared according to Stotland and Share's method [Canad. J. Physiol. Pharmacol. 52, 1114 (1974)]. That is, 1 mg of EWA was mixed with 20 mg of aluminum hydroxide gel and 0.5 ml of mixed vaccine of pertussis, diphtheria and tetanus, and the mixture was subcutaneously administered in four portions into rat's footpad. After 14 days, blood was sampled from the carotid artery, and the serum was separated from the sampled blood, and preserved under freezing at −80° C. The potency of the antiserumin in the homologous PCA for 48 hours was 1:32.

B) Homologous PCA test of rats for 48 hours

Groups each consisting of 3 rats were used, and 0.05 ml of anti-EWA rat serum diluted with a physiological saline solution to 8 times as much was incutaneously injected each at two positions of depilated back to make the animals passively sensitised. After 47 hours, the compound of the present invention, or its solution (physiological saline solution or CMC solution) was orally administered. One hour thereafter, 0.5 ml/100 g of 1% Evan's blue physiological saline solution containing 2 mg of the antigen EWA was administered into the tail vein, and 30 minutes thereafter, the animals were sacrificed by exsanguination. Then, the skins were stripped and the amount of leaked pigment at the blue-dyed parts was measured according to the Katayama et al method [Microbiol. Immunol. 22, 89 (1978)]. That is, the blue-dyed parts were cut out by scissors, and placed in test tubes containing 1 ml of 1N KOH and incubated at 37° C. for 24 hours. Then, 9 ml of a mixture of 0.6N phosphoric acid and acetone (5:13) was added thereto, and the mixture was shaked and centrifuged at 2,500 rpm for 10 minutes. Absorbancy of the supernatant at 620 μm was measured, and the amount of leaked pigment was quantitatively determined by the calibration curve prepared in advance. An average of measurements at the two position was made a value for one zooid, and inhibition rate for the individual zooid was calculated by the following formula:

$$\text{Inhibition rate (\%)} = \frac{\text{Average leaked amount of solvent-administered group} - \text{Leaked amount of test compound-administered group}}{\text{Average leaked amount of solvent-administered group}} \times 100$$

Cases where, the inhibition rate is 50% or higher, were regarded as positive PCA inhibition activity, and the minimum administered dosage, where a positive case was observed in at least one of three zooids was regarded as minimum effective dosage (MED). The results are shown in Table 5.

Acute Toxic Test

Groups each consisting of 3 dd, male mice having body weights of 20±1 g were used, and the compound of the present invention was administered orally (po: 300 mg/kg) or intraperitoneally (ip: 100 mg/kg). Mortality 7 days after the administration was observed to obtain MLD (minimum lethal dosage). The results are shown in Table 5.

Antiinflammatory Activity Test

Antiinflammatory activity was examined according to Rat carageenin paw edema [J. Pathol. 104, 15-29 (1971)]. Groups each consisting of three Wistar male rats weighing 150 g were used. The test compound was suspended in 0.3% aqueous CMC solution and the suspension was given orally. Sixty minutes later, 0.1 ml of 0.1% carageenin was subcutaneously injected in a hind paw to form carageenin paw edema.

The volume of paw was measured before the administration and 3 hours after the administration of carageenin with plethysmometer.

The ratio of the volume 3 hours after the administration to that before the administration of carageenin was calculated and each ratio is compared with the ratio of control group (0.3% CMC was administered) to give the edema inhibiting percentage. The results are shown in Table 6.

TABLE 5

Compound	Acute toxicity (MLD) mg/kg		Antiallergic Activity Number of positive zooids in one group of 3 zooids Dosage mg/kg						MED
	po	ip	100	10	1	0.1	0.01	0.001	mg/kg
3 (cis)	>300	>100	3/3	3/3	3/3	3/3	0/3	—	0.1
3' (trans)	>300	>100	3/3	2/3	1/3	1/3	0/3	—	0.1
5' (cis)	>300	>100	3/3	3/3	3/3	0/3	0/3	—	1
7' (cis:trans = 7:3)	>300	>100	3/3	2/3	1/3	0/3	—	—	1
9 (cis:trans = 91:9)	>300	>100	3/3	3/3	2/3	0/3	0/3	—	1
11' (trans)	>300	>100	2/3	1/3	0/3	0/3	—	—	10
13' (cis:trans = 7:93)	>300	>100	3/3	1/3	0/3	0/3	—	—	10
15' (trans)	—	—	3/3	0/3	0/3	0/3	—	—	100
20' (trans)	>300	>100	3/3	3/3	3/3	1/3	0/3	—	0.1
20	>300	>100	2/3	2/3	3/3	3/3	0/3	0/3	0.1

TABLE 5-continued

Compound	Acute toxicity (MLD) mg/kg po	Acute toxicity (MLD) mg/kg ip	Antiallergic Activity Number of positive zooids in one group of 3 zooids Dosage mg/kg 100	10	1	0.1	0.01	0.001	M E D mg/kg
(trans) 20	>300	>100	3/3	3/3	3/3	3/3	1/3	0/3	0.01
(cis) 22	>300	>100	3/3	3/3	2/3	1/3	0/3	—	0.1
(cis:trans = 92:8) 26'	>300	>100	3/3	3/3	2/3	0/3	—	—	1
(cis:trans = 12:88) 28'	>300	>100	3/3	3/3	3/3	2/3	2/3	0/3	0.01
(cis:trans = 37:63) 28	>300	>100	3/3	2/3	3/3	1/3	0/3	—	0.1
(cis) 28	>300	>100	3/3	3/3	2/3	2/3	1/3	0/3	0.01
(trans) 31'	>300	>100	3/3	3/3	3/3	1/3	0/3	—	0.1
(trans) 31	>300	>100	3/3	3/3	2/3	3/3	0/3	—	0.1
(trans) 31	300	>100	—	3/3	3/3	2/3	0/3	0/3	0.1
(cis) 33'	NT	NT	3/3	3/3	1/3	0/3	—	—	1
(cis) 35'	300>	100>	3/3	1/3	0/3	—	—	—	10
(cin:anti = 1:1) 37	300>	100>	3/3	3/3	0/3	—	—	—	10
(cin:anti = 8:92) 39	300>	100>	3/3	2/3	3/3	0/3	—	—	1
(cin:anti = 2:98) 41	300>	100>	3/3	2/3	1/3	0/3	—	—	1
(cin:anti = 3:97) 43'	300>	100>	3/3	2/3	0/3	0/3	—	—	10
cin:anti mixture 45'	300>	100>	3/3	3/3	2/3	0/3	—	—	1
(anti) 56'	>300	>100	3/3	3/3	3/3	1/3	0/3	—	0.1
(cis:trans = 87:13) 58	>300	>100	3/3	3/3	3/3	0/3	—	—	1
(cis:trans = 87:13) 60'	>300	>100	3/3	3/3	2/3	1/3	0/3	—	0.1
(cis)									

TABLE 6

Compound No.	Carageenin paw edema inhibiting percentage (%) (Average value in one group of 3 rats. 100 mg/kg oral administration)
37	51.6
39	50.2
41	38.7
45'	63.1
47	46.0
49	24.1

As is evidenced in Tables 5 and 6. Compound (I) and pharmaceutically acceptable salt thereof have PCA inhibiting activity and/or carageenin paw edema inhibiting activity.

PCA inhibiting activity is believed to be on the basis of an activity inhibiting liberation of chemical mediator such as histamine from fat skin cell. Therefore. Compound (I) and pharmaceutically acceptable salts thereof are believed to be useful for treating an allergic disease such as bronchus asthma which is caused by trachea

contractile activity of chemical mediator such as histamine.

On the other hand, carageenin paw edema inhibiting activity is believed to be on the basis of prostaglandin biosynthesis inhibiting activity. Thus, Compound (I) and pharmaceutically acceptable salts thereof are believed to be useful for treating an acute inflammation and rheumatism which are ascribed to excessive prostaglandin.

Compound (I) includes a compound having both antiallergic and antiinflammatory activities described above which is useful for the treatment of allergic diseases accompanied by inflammation.

In view of the pharmacological activity of Compound (I), Compound (I) can be used in various medicament forms for the administration purposes.

The present medicament composition can be prepared by uniformly mixing an effective amount of a free Compound (I) or a pharmaceutically acceptable salt thereof as an active component with a pharmaceutically

acceptable carrier or excipient. The carrier can take a wide range of forms in accordance with a desirable medicament form for the administration. These medicament compositions are desirably in a unit dosage form suitable for the oral administration or injection administration. In the preparation of a composition in the oral dosage form, any useful, pharmaceutically acceptable carrier can be used. For example, an oral liquid preparation such as a suspended medicament or syrup medicament can be prepared using water; sugars such as sucrose, sorbitol, fructose, etc.; glycols such as polyethylene glycol, propylene glycol, etc.; oils such as sesame oil, olive oil, soybean oil, etc.; antiseptics such as alkyl parahydroxybenzoate, etc.; and flavors such as strawberry flavor, peppermint, etc. Powder, pills, capsules and tablets can be prepared using an excipient such as lactose, glucose, sucrose, mannitol, etc.; a disintegrator such as starch, sodium alginate, etc.; a lubricant such as magnesium stearate, talc, etc.; a binder such as polyvinyl alcohol, hydroxypropylcellulose, gelatin, etc.; a surfactant such as fatty acid esters; and a plasticizer such as glycerine, etc. Tablets and capsules are the most useful, oral unit dosage forms because of easy administration. To prepare tablets and capsules, solid carriers for medicament are used. Injection solution can be prepared using a carrier consisting of a salt solution, a glucose solution or a mixture of the salt solution and the glucose solution. The effective dosage of Compound (I) is 1 to 20 mg/kg/day for a human being, and number of administration is 3 to 4 per day.

Examples and Reference Examples are given below:

REFERENCE EXAMPLE 1

(Raw material 1) Methyl 11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate

In this example, 348.9 g of sodium salt of methyl p-hydroxybenzoate, 402.4 g of phthalide and 200 g of sodium chloride are mixed with one another and stirred at 150° C. for 6 hours. After completion of the reaction, the mixture is cooled until the temperature is brought back to room temperature, 4 l of aqueous 10% acetic acid solution is added thereto and the mixture is allowed to stand at room temperature overnight. After stirring the mixture at room temperature for 3 hours, deposited crystals are separated by filtration, and 6 l of water is added thereto. After stirring the mixture at room temperature for 30 minutes, the deposited crystals are separated by filtration. After the addition of 3 l of toluene to the crystals, the mixture is stirred at room temperature for one hour. The crystals are separated by filtration and dried over heating under reduced pressure to yield 393.9 g of 2-(4-methoxycarbonylphenoxy) methyl benzoic acid.

IR (KBr disk): 3400, 1700, 1610, 1260, 1235 cm^{-1} The thus obtained 2-(4-methoxycarbonylphenoxy) methyl benzoic acid (392.7 g) is suspended in 5.0 l of methylene chloride and 266.0 g of trifluoroacetic anhydride is added thereto. After stirring the mixture at room temperature for one hour, 19.4 g of boron trifluoride-ethylether complex is added thereto and the mixture is stirred at room temperature for two hours. The reaction solution is poured into ice water. After an organic solvent layer is separated from the mixture, the organic layer is washed with diluted aqueous sodium hidroxide solution and water, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to

obtain 335.3 g of methyl 11-oxodibenz[b,e]oxepin-2-carboxylate as a white crystal.

Melting point and elementary analysis are shown in Table 7.

IR (KBr disk): 1710, 1650, 1610, 1250, 1010 cm^{-1}

NMR ($CDCl_3$, δ, ppm): 3.84(s, 3H), 5.14(s, 2H), 6.87–8.93(m, 7H)

REFERENCE EXAMPLES 2–5

(Raw material 2) 11-Oxo-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid

(Raw material 3) 11-Oxo-6,11-dihydrodibenz[b,e]oxepin-3-acetic acid

(Raw material 4) 2-(11-Oxo-6,11-dihydrodibenz[b,e]oxepin-2-yl)-propionic acid

(Raw material 5) 3-(11-Oxo-6,11-dihydrodibenz[b,e]oxepin-2-yl)-propionic acid

Raw materials 2–5 are produced by respectively substituting p-hydroxyphenyl acetic acid, m-hydroxyphenyl acetic acid, 2-(p-hydroxyphenyl)-propionic acid and 3-(p-hydroxyphenyl)-propionic acid for methyl p-hydroxybenzoate in Reference example 1.

Melting points and elementary analyses thereof are shown in Table 7.

REFERENCE EXAMPLE 6

(Raw material 6) Methyl 11-methylene-6,11-dihydrodibenz-[b,e]oxepin-2-carboxylate

In 100 ml of tetrahydrofuran is suspended 25 g of methyltriphenylphosphonium bromide and 40 ml of 1.6 N-n-butyl lithium helium hexane solution is dropwise added thereto under a nitrogen atmosphere and ice-cooling. After stirring the mixture under ice-cooling for 30 minutes, a solution obtained by dissolving 15 g of methyl 11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate in 250 ml of tetrahydrofuran is dropwise added thereto and the mixture is stirred at room temperature for two hours. The solvent is distilled away under reduced pressure and the residue is purified by column chromatography on silica gel (eluent: hexane:ethyl acetate = 3:1) to obtain 3.7 g of the desired product as a colorless oily matter.

NMR ($CDCl_3$, δ, ppm): 3.83(s, 3H), 5.15(s, 2H), 5.29 (s, 1H), 5.74(s, 1H), 6.69–8.22(m, 7H)

Melting point and elementary analysis are shown in Table 7.

REFERENCE EXAMPLE 7

(Raw material 7) Methyl 11-methylene-6,11-dihydrodibenz-[b,e]oxepin-2-acetate

The desired product is obtained by substituting 11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid for methyl 11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate in Reference example 6.

Colorless oily matter

NMR ($CDCl_3$, δ, ppm): 3.48(s, 2H), 3.61(s, 3H), 5.05 (s, 2H), 5.20(s, 1H), 5.62(s, 1H), 6.59–7.43 (m, 7H)

IR (neat, cm^{-1}): 2950, 1740, 1615, 1490, 1010

Melting point and elementary analysis are shown in Table 7.

REFERENCE EXAMPLE 8

(Raw material 8) 11-Methylene-6,11-dihydrodibenz[b,e]-oxepin-2-acetic acid

To a mixed solvent of 200 ml of methanol and 50 ml of 2N-aqueous sodium hydroxide solution is added 2.9 g

of methyl 11-methylene-6,11-dihydrodibenz[b,e]oxepin-2-acetate (raw material 7, Reference example 7) and the mixture is heated at reflux for two hours. After allowing the mixture to stand for cooling, the mixture is concentrated under reduced pressure, and the pH of the mixture is adjusted to 1.0 with aqueous 4N-hydrochloric acid solution. The mixture is extracted with 500 ml of ethyl acetate, washed with aqueous 1N-hydrochloric acid solution and saturated aqueous sodium chloride solution in order and dried over anhydrous sodium sulfate. The solvent is distilled away under reduced pressure and the resultant crude product is crystallized from hexane to obtain 2.7 g of the desired product as a white solid.

NMR (DMSO-d_6+D_2O, δ, ppm): 3.45(s, 2H), 5.02(s, 2H), 5.16(s, 1H), 5.60(s, 1H), 6.45–7.44(m, 7H)

Melting point and elementary analysis are shown in Table 7.

REFERENCE EXAMPLE 9

(Raw material 9) Methyl 11-methylene-6,11-dihydrodibenz-[b,e]oxepin-3-acetate

The desired product is obtained by substituting 11-oxo-6,11-dihydrodibenz[b,e]oxepin-3-acetic acid for methyl 11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate in Reference example 6.

REFERENCE EXAMPLE 10

(Raw material 10) 11-Methylene-6,11-dihydrodibenz[b,e]oxepin-3-acetic acid

The desired product is obtained by substituting methyl 11-methylene-6,11-dihydrodibenz[b,e]oxepin-3-acetate for methyl 11-methylene-6,11-dihydrodibenz[-b,e]oxepin-2-acetate in Reference example 8.

TABLE 7

Raw material	Melting point (°C.)	Elementary analysis (%) or mass spectrum		
1	128–129	as $C_{16}H_{12}O_4$		
			C	H
	(Isopropyl	Calculated	71.63	4.51
	ether)	Found	71.55	4.48
2	130–132	as $C_{16}H_{12}O_4$		
			C	H
	(Ethyl	Calculated	71.63	4.51
	acetate)	Found	71.86	4.55
3	111–114	as $C_{16}H_{12}O_4$		
			C	H
	(Ethyl	Calculated	71.63	4.51
	acetate)	Found	71.53	4.66
4	Syrup	as $C_{17}H_{14}O_4$ (M + 282)		
5	144–145	as $C_{17}H_{14}O_4$		
			C	H
	(Water)	Calculated	72.33	5.00
		Found	72.45	5.20
6	Syrup	as $C_{17}H_{14}O_3$ (M + 266)		
7	Syrup	as $C_{18}H_{16}O_3$ (M + 280)		
8	162–163	as $C_{17}H_{14}O_3$		
			C	H
	(Water)	Calculated	76.68	5.30
		Found	76.29	5.16

REFERENCE EXAMPLE 11

(Reagent 1)
(3-Dimethylaminopropyl)-triphenylphosphonium bromide hydrobromide

In this example, 350.0 g of triphenylphosphine and 270.0 g of dibromopropane are suspended in 700 ml of toluene and the suspension is heated at reflux for 25 hours. After allowing the suspension to stand for cooling, the formed product is separated by filtration and washed with 2 l of toluene to obtain 550.0 g of (3-bromopropyl)-triphenylphosphonium bromide hydrobromide having m.p. 233–234° C.

Then, 100.0 g of (3-bromopropyl)-triphenylphosphonium bromide hydrobromide is suspended in 500 ml of ethanol, and 300 ml of 50% aqueous dimethylamine solution is added thereto. After heating the mixture at reflux for 10 minutes, the mixture is allowed to stand for cooling. The solvent is distilled away under reduced pressure and the resultant crude product is recrystallized from ethanol to obtain 64.0 g of the desired product having the physicochemical properties as identified in Table 8.

REFERENCE EXAMPLES 12–14

(Reagent 2) (3-Diethylaminopropyl)-triphenylphosphonium bromide hydrobromide.$\frac{1}{3}$ hydrate

(Reagent 3) (4-Dimethylaminobutyl)-triphenylphosphonium bromide hydrobromide

(Reagent 4) (3-Pyrrolidinopropyl)-triphenylphosphonium bromide hydrobromide.$\frac{1}{2}$ hydrate

The above-captioned compounds are prepared according to the same manner as in Reference example 11 and the physicochemical properties are shown in Table 8.

TABLE 8

Reagent	Melting point (°C.)	Elementary analysis (%)			
1	287–289 (Ethanol)	as $C_{23}H_{28}NPBr_2$			
			C	H	N
		Calculated	54.24	5.54	2.75
		Found	54.12	5.63	2.93
2	228–230 (Isopropanol)	as $C_{25}H_{32}NPBr_2.\frac{1}{3}H_2O$			
			C	H	N
		Calculated	55.33	6.05	2.58
		Found	55.31	6.19	2.68
3	255–257 (Isopropanol)	as $C_{24}H_{30}NPBr_2$			
			C	H	N
		Calculated	55.09	5.78	2.68
		Found	55.04	5.91	2.62
4	291–293 (Ethanol)	as $C_{25}H_{30}NPBr_2.\frac{1}{2}H_2O$			
			C	H	N
		Calculated	55.17	5.74	2.57
		Found	55.18	5.95	2.66

EXAMPLE 1

Ethyl
11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate (Compound 2)

Process A:
N-(1,1-dimethyl-2-hydroxyethyl)-11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-carboxamide

In this process, 12.5 g of 6,11-dihydro-11-oxodibenz[b,e]oxepin-2-carboxylic acid is dissolved in 300 ml of methylene chloride and 8.9 g of thionyl chloride is dropwise added to the solution under ice-cooling. After stirring the mixture at room temperature for two hours,

the solvent is distilled away under reduced pressure. To the obtained residue are added 100 ml of toluene and 32.4 g of 2-amino-2-methyl-propanol, and the mixture is stirred at 50° C. for 3 hours.

The mixture is extracted with 500 ml of ethyl acetate, and washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution in order. The mixture is dried over anhydrous sodium sulfate and the solvent is distilled away under reduced pressure. The crude product is recrystallized from toluene to obtain 8.3 g of the desired product as a white crystal.

Melting point: 155–159° C.

NMR ($CDCl_3$ + DMSO-d_6, δ, ppm): 1.38(s, 6H), 3.53(s, 2H), 5.25(s, 2H), 6.91–8.68(m, 7H)

Process B:

2-(4,4-Dimethyl-2-oxazoline-2-yl)-11-oxo-6,11-dihydrodibenz[b,e]oxepin

In this process, 8.0 g of N-(1,1-dimethyl-2-hydroxyethyl)-11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-carboxamide is suspended in 100 ml of methylene chloride. To the suspension is added 3.6 g of thionyl chloride under a nitrogen atmosphere and ice-cooling and the mixture is stirred at room temperature for one hour. To the mixture is added 300 ml of methylene chloride, and the mixture is washed with saturated aqueous sodium bicarbonate solution and dried over anhydrous magnesium sulfate. The solvent is distilled away under reduced pressure and the residue is purified by column chromatography on silica gel (eluent: hexane:ethyl acetate=2:1). The resultant crude product is recrystallized from hexane to obtain 6.3 g of the desired product as a white crystal.

Melting point: 122° C.

NMR ($CDCl_3$, δ, ppm): 1.37(s, 6H), 4.06(s, 2H), 5.14(s, 2H), 6.84–8.89(m, 7H)

Elementary analysis (%): as $C_{19}H_{17}O_3N$:

Calculated: C 74.25, H 5.58, N 4.56,

Found: C 74.23, H 5.55, N 4.59.

Process C:

11-(3-Dimethylaminopropyl)-11-hydroxy-2-(4,4-dimethyl-2-oxazoline-2-yl)-6,11-dihydrodibenz[b,e]oxepin

To a solution of 3-dimethylaminopropyl magnesium chloride obtained by reacting 1.2 g of magnesium with 6.0 g of 3-dimethylaminopropyl chloride in 80 ml of tetrahydrofuran under a nitrogen atmosphere using dibromoethane as a catalyst is dropwise added under ice-cooling 80 ml of tetrahydrofuran solution of 7.6 g of 2-(4,4-dimethyl-2-oxazoline-2-yl)-11-oxo-6,11-dihydrodibenz[b,e]oxepin.

After stirring the mixture at room temperature overnight, aqueous ammonium chloride solution is added thereto and then the mixture is neutralized with aqueous 4N-hydrochloric acid solution. The solvent is distilled away under reduced pressure. To the residue is added aqueous 4N-hydrochloric acid solution to adjust the pH of the solution to 1. After washing the mixture with 200 ml of diethyl ether, aqueous 10N-sodium hydroxide solution is added to adjust the pH of the mixture to 13. The mixture is extracted with 200 ml of methylene chloride and the extract is washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution in order. After drying the solution over anhydrous sodium sulfate, the solvent is distilled away under reduced pressure. The residue is

purified by column chromatography on silica gel (eluent: hexane:ethyl acetate triethylamine=10:10:1). The resultant crude product is triturated with isopropyl ether to obtain 6.1 g of the desired product as a white solid.

Melting point: 166–167° C.

NMR ($CDCl_3$, δ, ppm): 1.30(s, 8H), 2.18(s, 8H), 3.98 (s, 2H), 4.97 and 5.46(ABq, J=15.1 Hz, 2H), 6.65–8.49(m, 7H)

Process D: Ethyl 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate

In this process, 6.1 g of 11-(3-dimethylaminopropyl)-11-hydroxy-2-(4,4-dimethyl-2-oxazoline-2-yl)-6,11-dihydrodibenz[b,e]oxepin is dissolved in 300 ml of ethanol. To the solution are added 0.6 g of p-toluenesulfonic acid and 30 ml of water and the mixture is heated at reflux for 4 hours. The solvent is distilled away under reduced pressure to obtain a crude product of 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylic acid. The crude product is dissolved in 300 ml of ethanol and 20 ml of concentrated sulfuric acid is added thereto. The mixture is heated at reflux for 15 hours.

The solvent is distilled away under reduced pressure. To the resultant residue is added 200 ml of water and the mixture is washed with diethyl ether. The pH of the mixture is adjusted to 12.0 with aqueous 10N-sodium hydroxide solution and the mixture is extracted with 300 ml of methylene chloride. The extract is washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution in order. After drying the extract over anhydrous sodium sulfate, the solvent is distilled away under reduced pressure and the resultant residue is purified by column chromatography on silica gel (eluent: ethyl acetate:triethylamine = 10:1) to obtain 1.4 g of the desired product as a colorless oily matter.

IR (neat, cm^{-1}): 2950, 2775, 1715, 1250, 1120, 1010

Mass spectrum (m/z): 351 (M^-)

EXAMPLE 2

11-(3-Dimethylaminopropylidene)-2-(2-triphenylmethyloxymethyl)-6,11-dihydrodibenz[b,e]oxepin (Compound 32)

Process A: 11-Hydroxy-2-(2-hydroxyethyl)-6,11-dihydrodibenz[b,e]oxepin

In this process, 20 g of methyl 11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-acetate is dissolved in 500 ml of tetrahydrofuran. To the solution is added 6.0 g of lithium alminium hydroxide and the mixture is stirred at room temperature for one hour. After decomposing an excess of the reagent by the addition of water to the solution, the mixture is filtered to remove an inorganic salts and the filtrate is concentrated to dryness under reduced pressure to obtain 17.7 g of the desired product as a white solid.

Melting point: 132–136° C.

NMR ($CDCl_3$ + DMSO-d_6 + D_2O, δ, ppm): 2.59(t, 2H, J=6.8Hz), 3.55(t,2H, J=6.8Hz), 4.89 and 5.71(ABq, 2H, J=12.6Hz), 5.60(s, 1H), 6.46–7.49(m, 7H)

Process B:
11-Hydroxy-2-(2-triphenylmethyloxyethyl)-6,11-dihydrodibenz[b,e]oxepin

In this process, 17.2 g of 11-hydroxy-2-(2-hydroxyethyl)-6,11-dihydrodibenz[b,e]oxepin is dissolved in 50 ml of pyridine. To the solution is added 30 g of triphenylchloromethane and the mixture is stirred at 50° C. for 5 hours. After adding water and stirring the mixture for 2 hours, the solvent is distilled away under reduced pressure. The mixture is extracted with 1000 ml of ethyl acetate, washed with saturated aqueous sodium chloride solution, and dried over anhydrous sodium sulfate. The solvent is distilled away under reduced pressure and the resultant residue is purified by column chromatography on silica gel (eluent: hexane:ethyl acetate = 3:1) to obtain 21.7 g of the desired product as a colorless amorphous.

NMR ($CDCl_3+D_2O$, δ, ppm): 2.47–2.95(m, 2H), 2.96–3.45(m, 2H), 4.87 and 5.71(ABq, 2H, J = 13.2Hz), 5.43(s, 1H), 6.33–7.51(m, 22H)

Process C:
11-Oxo-2-(2-triphenylmethyloxyethyl)-6,11-dihydrodibenz[b,e]oxepin

In this process, 10 g of 11-hydroxy-2-(2-triphenylmethyloxyethyl)-6,11-dihydrodibenz[b,e]oxepin is dissolved in a solution comprising 800 ml of acetone, 1000 ml of water, 20 ml of saturated aqueous magnesium sulfate solution and 0.2 g of disodium phosphate. To the solution is dropwise added 2.6 g of aqueous sodium permanganate solution and the mixture is stirred at room temperature for 4.5 hours. Then, 100 ml of methanol is added thereto and the mixture is heated at reflux for 3 hours. After allowing the mixture to stand for cooling, the mixture is filtered and the filtrate is extracted with 1000 ml of ethyl acetate, washed with saturated aqueous sodium chloride solution and dried over anhydrous sodium sulfate. The solvent is distilled away under reduced pressure and the resultant crude product is recrystallized from isopropanol to obtain 8.0 g of the desired product having melting point of 132–134° C. as a white crystal.

Elementary analysis (%): as $C_{35}H_{28}O_3$
Calculated: C 84.65, H 5.68.
Found: C 84.56, H 5.67.
NMR ($CDCl_3$, δ, ppm): 2.61–3.04(m, 2H), 3.05–3.46 (m, 2H), 5.01(s, 2H), 6.63–8.07(m, 22H)

Process D:
11-(3-Dimethylaminopropyl)-11-hydroxy-2-(2-triphenylmethyloxyethyl)-6,11-dihydrodibenz[b,e]oxepin

To a solution of 3-dimethylaminopropyl magnesium chloride obtained by reacting 0.2 g of magnesium with 1.0 g of 3-dimethylaminopropyl chloride in 10 ml of tetrahydrofuran under a nitrogen atmosphere using dibromoethane as a catalyst, is dropwise added a solution obtained by dissolving 2.0 g of 11-oxo-2-(2-triphenylmethyloxyethyl)-6,11-dihydrodibenz[b,e]oxepin in 10 ml of tetrahydrofuran under ice cooling and the mixture is stirred at room temperature for one day. Aqueous ammonium chloride solution is added thereto and the pH of the mixture is adjusted to 7.0 with aqueous 4N-hydrochloric acid solution. The solvent is distilled away under reduced pressure. The mixture is extracted with 200 ml of methylene chloride and washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution

in order. After drying the extract over anhydrous sodium sulfate, the solvent is distilled away under reduced pressure. The resultant residue is purified by column chromatography on silica gel (eluent: hexane:ethyl acetate:triethylamine = 10:10:1) to obtain 1.2 g of the desired product as a colorless amorphous.

NMR ($CDCl_3$, δ, ppm): 0.85–1.83(m, 4H), 2.08(s, 6H), 2.67–3.44(m, 6H), 4.94 and 5.36(ABq, 2H, J = 15.8Hz), 6.63–8.13(m, 22H)

Mass spectrum (m/z): 583 (M^+)

Process E:

11-(3-Dimethylaminopropylidene)-2-(2-triphenylmethyloxyethyl)-6,11-dihydrodibenz[b,e]oxepin

In this process, 1.2 g of 11-(3-dimethylaminopropyl)-11-hydroxy-2-(2-triphenylmethyloxyethyl)-6,11-dihydrodibenz[b,e]oxepin is dissolved in 50 ml of pyridine. To the solution is dropwise added 0.8 g of phosphorusoxychloride under a nitrogen atmosphere and ice-cooling. After stirring the mixture at room temperature for one hour, the solvent is distilled away under reduced pressure. The residue is extracted with 100 ml of methylene chloride, and washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution in order. After drying the mixture over anhydrous sodium sulfate, the solvent is distilled away under reduced pressure. The resultant residue is purified by column chromatography on silica gel (eluent: hexane:ethylacetate:triethylamine = 10:10:1) to obtain 0.82 g of the desired product as a colorless oily matter.

NMR ($CDCl_3$, δ, ppm): 2.16(s, 6H), 2.30–2.40(m, 4H), 2.79(t, 2H, J = 6Hz), 3.24(t, 2H, J = 6Hz), 5.97 (t, 1H, J = 7Hz), 6.60–7.40(m, 22H), (trans form)

Mass spectrum (m/z): 565 (M^+)

EXAMPLE 3

11-(3-Dimethylaminopropylidene)-2-(2-hydroxyethyl)-6,11-dihydrodibenz[b,e]oxepin (Compound 31)

In this example, 0.92 g of 11-(3-dimethylaminopropylidene)-2-(2-triphenylmethyloxyethyl)-6,11-dihydrodibenz[b,e]oxepin is dissolved in a mixed solvent of 20 ml of water and 20 ml of dioxane. To the solution is added 60 mg of p-toluene sulfonic acid and the mixture is heated at reflux for two hours. The solvent is distilled away under reduced pressure and the residue is extracted with 200 ml of ethylacetate, washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium hydrochloride solution in oder and dried over anhydrous sodium sulfate. The solvent is distilled away under reduced pressure. The resultant residue is purified by column chromatography on silica gel (eluent: ethylacetate triethylamine = 10:1) to obtain 0.4 g of the desired product.

Cis form white solid,

Melting point: 100–102° C. (diethylether)

NMR ($CDCl_3$, δ, ppm): 2.32(s, 6H), 2.30–2.70(m, 4H), 2.76(t, 2H, J = 6Hz), 3.78(t, 2H, J = 6Hz), 5.66(t, 1H, J = 7Hz), 6.80–7.40(m, 7H)

Mass spectrum: 323 (M^+)

Trans form white solid,

Melting point: 96°–97° C. (diethylether)

NMR ($CDCl_3$, δ, ppm): 2.21(s, 6H), 2.30–2.70(m, 4H), 2.76(t, 2H, J = 6Hz), 3.78(t, 2H, J = 6Hz), 6.01(t, 1H, J = 7Hz), 6.68–7.40(m, 7H)

Mass spectrum (m/z): 323 (M^-)

EXAMPLE 4

11-(3-Dimethylaminopropylidene)-6.11-dihydrodibenz [b,e]oxepin-2-acetic acid (Compound 20)

In this Example, 2.2 g of 11-(3-dimethylaminopropylidene)-2-(2-hydroxyethyl)-6,11-dihydrodibenz[b,e]oxepin is dissolved in 100 ml of acetone. The Jones reagent is added to the solution until the reaction solution shows an orange color and the mixture is stirred at room temperature for one hour. Sodium bicarbonate is added thereto and an inorganic substance is removed by filtration. The solvent of the filtrate is distilled away under reduced pressure to obtain the desired product. The physicochemical properties of the product coincide with those of the product obtained in Example 35.

EXAMPLE 5

Methyl 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b.e]oxepin-2-carboxylate (Compound 1)

In this Example, 45 g of (3-dimethylaminopropyl)triphenylphosphonium bromide hydrobromide is suspended in 200 ml of tetrahydrofuran under a nitrogen atmosphere and 82 ml of 1.6N-n-butyl lithium hexane solution is added thereto under ice-cooling. The mixture is stirred under ice-cooling for one hour. To the mixture is dropwise added under ice-cooling a solution obtained by dissolving 10 g of methyl 11-oxo-6,11-dihydrodibenz[b.e]oxepin-2-carboxylate in 200 ml of tetrahydrofuran. After stirring the mixture at room temperature for 2 hours, the mixture is extracted with 800 ml of ethyl acetate. After washing the extract with saturated aqueous sodium chloride solution and drying the extract over anhydrous sodium sulfate, the solvent is distilled away under reduced pressure. The residue is purified by column chromatography on silica gel (eluent: hexane:ethyl acetate:triethylamine = 10:10:1) to obtain 2.0 g of trans form and 5.6 g of cis form of the desired product.

Cis form: NMR ($CDCl_3$, δ, ppm): 2.23(s, 6H), 2.17–2.81(m, 4H), 5.28(bs, 2H), 5.61(t, 1H), 6.80–8.10(m, 7H)

Trans form: NMR ($CDCl_3$, δ, ppm): 2.15(s, 6H), 2.17–2.81(m, 4H), 5.00–5.50(broad, 2H), 6.06 (t, 1H), 6.70–8.10(m, 7H)

EXAMPLE 6

Methyl 11-(3-diethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate (Compound 4)

The desired product is obtained by substituting (3-diethylaminopropyl)-triphenylphosphonium bromide hydrobromide.½ hydrate for (3-dimethylaminopropyl)-triphenylphosphonium bromide hydrobromide in Example 5.

EXAMPLE 7

Methyl 11-(3-pyrrolidinopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate (Compound 6)

The desired product is obtained by substituting (3-pyrrolidinopropyl)-triphenylphosphonium bromide hydrobromide.½ hydrate for (3-dimethylaminepropyl)-triphenylphosphonium bromide hydrobromide in Example 5.

EXAMPLE 8

Methyl 11-(4-dimethylaminobutylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate (Compound 8)

The desired product is obtained by substituting (4-dimethylaminopropyl)-triphenylphosphonium bromide hydrobromide for (3-dimethylaminopropyl)-triphenylphosphonium bromide hydrobromide in Example 5.

EXAMPLE 9

Methyl 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetate (Compound 18)

In this example, 48 g of (3-dimethylaminopropyl)-triphenylphosphonium bromide hydrobromide is suspended in 200 ml of tetrahydrofuran under a nitrogen atmosphere and 80 ml of 1.6N-n-butyl lithium hexane solution is added thereto under ice-cooling. The mixture is stirred under ice-cooling for one hour. A solution obtained by dissolving 5.0 g of 11-oxo-6,11-dihydrodibenz [b,e]oxepin-2-acetic acid in 120 ml of tetrahydrofuran is dropwise added under ice-cooling. After stirring the mixture at room temperature for two hours, the solvent is distilled away under reduced pressure. Then, 200 ml of water is added to the residue and the mixture is washed with 200 ml of diethyl ether. The pH of the mixture is adjusted to 1 with aqueous 4N-hydrochloric acid solution and the mixture is washed with diethyl ether.

Then, aqueous 10N-sodium hydrooxide solution is added thereto to adjust the pH of the mixture to 7 and the solvent is distilled away under reduced pressure. The resultant residue is dissolved in 400 ml of methanol and 5 g of p-toluene sulfonic acid is added thereto. After heating the mixture at reflux for two hours, the solvent is distilled away under reduced pressure. The residue is extracted with 300 ml of ethyl acetate, washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution in order and dried over anhydrous sodium sulfate.

The solvent is distilled away under reduced pressure and the resultant residue is purified by column chromatography on silica gel (eluent: hexane:ethyl acetate:triethylamine = 10:10:1) to obtain 4.0 g of the desired product as a colorless oily matter.

Cis form

NMR ($CDCl_3$, δ, ppm): 2.06–2.67(m, 4H), 2.16(s, 6H), 3.46(s, 2H), 3.58(s, 3H), 5.08(bs, 2H), 5.69 (t, 1H, J = 7Hz), 6.53–7.30(m, 7H)

Trans form

NMR ($CDCl_3$, δ, ppm): 2.06–2.67(m, 4H), 2.16(s, 6H), 3.46(s, 2H), 3.58(s, 3H), 5.08(bs, 2H), 6.06 (t, 1H, J = 7Hz), 6.53–7.30(m, 7H)

EXAMPLE 10

Methyl 11-(4-dimethylaminobutylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetate (Compound 21)

The desired product is obtained by substituting (4-dimethylaminobutyl)-triphenylphosphonium bromide hydrobromide for (3-dimethylaminopropyl)-triphenylphosphonium bromide hydrobromide in Example 9.

EXAMPLE 11

Methyl 11-(3-pyrrolidinopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetate (Compound 23)

The desired product is obtained by substituting (3-pyrrolidinopropyl)-triphenylphosphonium bromide hydrobromide. ½ hydrate for (3-dimethylaminopropyl)-triphenylphosphonium bromide hydrobromide in Example 9.

EXAMPLE 12

Methyl 3-[11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-yl]-propionate (Compound 27)

The desired product is obtained by substituting 3-(11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-yl)-propionic acid for 11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid in Example 9.

EXAMPLE 13

Methyl 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-3-acetate (Compound 29)

The desired product is obtained by substituting 11-oxo-6,11-dihydrodibenz[b,e]oxepin-3-acetic acid for 11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid in Example 9.

EXAMPLE 14

Methyl 11-(2-dimethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-acetate (Compound 36)

In this example, 22.0 g of methyl 11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-acetate and 68.7 g of N,N-dimethylethylenediamine are dissolved in 700 ml of dried benzene. To the solution is dropwise added a solution of 17.2 ml of titanium tetrachloride in 40 ml of dried benzene and the mixture is stirred at room temperature overnight. A saturated aqueous sodium bicarbonate solution is added thereto. After removing an insoluble solid by filtration, the filtrate is extracted with 500 ml of ethylacetate, washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution in order, and dried over anhydrous sodium sulfate. The solvent is distilled away under reduced pressure and the residue is purified by column chromatography on silica gel with ethylacetate/triethylamine (10/1) as an eluent to obtain 13.8 g of the desired product as a colorless oily matter.

NMR ($CDCl_3$, δ, ppm): 2.14(s, 6H), 2.63(t, 2H, J=6.9Hz),
3.51(s, 2H), 3.58(s, 3H), 3.38–3.80
(m, 2H), 5.04(bs, 2H), 6.56–7.60(m, 7H)

IR (neat, cm^{-1}) 2950, 1740, 1630, 1305, 1015

Mass spectrum (m/z): 352 (M^-)

EXAMPLE 15

Methyl-11-(2-diethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate (Compound 34)

The desired product is obtained by substituting methyl 11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate for methyl 11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-acetate in Example 14 as a colorless oily matter.

Mass spectrum (m/z): 366 (M^+) for $C_{22}H_{26}O_3N_2$

EXAMPLE 16

Ethyl
11-(2-diethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-acetate (Compound 38)

The desired product is obtained by substituting N,N-diethylethylenediamine for N,N-dimethylethylenediamine in Example 14 as a colorless oily matter.

Mass spectrum (m/z): 380 (M^+) for $C_{23}H_{28}O_3N_2$

EXAMPLE 17

Methyl
11-(3-dimethylaminopropyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-acetate (Compound 40)

The desired product is obtained by substituting N,N-dimethylpropylenediamine for N,N-dimethylethylenediamine in Example 14 as a colorless oily matter.

Mass spectrum (m/z): 366 (M^+) for $C_{22}H_{26}O_3N_2$

EXAMPLE 18

Methyl
3-[11-(2-dimethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-yl]-propionate (Compound 42)

The desired product is obtained by substituting 3-(11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-yl)-propionic acid for methyl 11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-acetate in Example 16 as a colorless oily matter.

Mass spectrum (m/z): 394 (M^+) for $C_{24}H_{30}O_3N_2$

EXAMPLE 19

Methyl
2-[11-(2-dimethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-yl]-propionate (Compound 44)

The desired product is obtained by substituting 2-(11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-yl)-propionic acid for methyl 11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-acetate in Example 14 as a colorless oily matter.

Mass spectrum (m/z): 366 (M^+) for $C_{22}H_{26}O_3N_2$

EXAMPLE 20

Methyl
11-(2-dimethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-3-acetate (Compound 46)

The desired product is obtained by substituting 11-oxo-6,11-dihydrodibenz[b,e]oxepin-3-acetic acid for methyl 11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-acetate in Example 14 as a colorless oily matter.

Mass spectrum (m/z): 352 (M^+) for $C_{21}H_{24}O_3N_2$

EXAMPLE 21

Methyl
11-(3-dimethylaminopropyl)imino-6,11-dihydrodibenz[b,e]oxepin-3-acetate (Compound 48)

The desired product is obtained by substituting 11-oxo-6,11-dihydrodibenz[b,e]oxepin-3-acetic acid for 11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid in Example 17 as a colorless oily matter.

Mass spectrum (m/z): 366 (M^+) for $C_{22}H_{26}O_3N_2$

EXAMPLE 22

Methyl
11-[2-(4-methylpiperazino)ethylidene]-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate (Compound 10)

In this example, 1.5 ml of 4-methylpiperazine and 0.37 g of p-formaldehyde are dissolved in 100 ml of tetrachloroethane. To the solution is dropwise added 5 ml of trifluoroacetic acid. After stirring the mixture at 60° C. for 2 hours, a solution obtained by dissolving 1.8 g of methyl 11-methylene-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate in 30 ml of tetrachloroethane is dropwise added thereto and the mixture is stirred at 90° C. for 3 hours.

The mixture is concentrated to dryness under reduced pressure and aqueous 4N-hydrochloric acid solution is added to the residue to adjust the pH to 1. After washing the solution with diethylether, aqueous 10N-sodium hydroxide solution is added thereto to adjust the pH to 13. The mixture is extracted with 200 ml of methylene chloride, washed with saturated aqueous sodium chloride solution and dried over anhydrous sodium sulfate. The solvent is distilled away under reduced pressure. The residue is purified by column chromatography on silica gel (eluent: hexane:ethyl acetate:triethylamine = 5:5:1) to obtain 2.2 g of the desired product as a colorless oily matter.

Cis form: NMR ($CDCl_3$, δ, ppm): 2.24(s, 3H), 2.45(s, 8H), 2.94–3.32(m, 2H), 3.84(s, 3H), 5.22(bs, 2H), 5.85(t, 1H, J = 6.8Hz), 6.66–8.07(m, 7H)

Mass spectrum (m/z): 378 (M^+)

Trans form: NMR ($CDCl_3$, δ, ppm): 2.24(s, 3H), 2.45(s, 8H), 2.94–3.32(m, 2H), 3.84(s, 3H), 5.22(bs, 2H), 6.22(t, 1H, J = 6.8Hz)

Mass spectrum (m/z): 378 (M^+)

EXAMPLE 23

Methyl
11-(2-morpholinoethylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate (Compound 12)

The desired product is obtained by substituting morpholine for 4-methylpiperazine in Example 22.

EXAMPLE 24

Methyl
11-(2-thiomorpholinoethylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate (Compound 14)

The desired product is obtained by substituting thiomorpholine for 4-methylpiperazine in Example 22.

EXAMPLE 25

Methyl
11-(2-pyrrolidinoethylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate (Compound 16)

The desired product is obtained by substituting pyrrolidine for 4-methylpiperazine in Example 22.

EXAMPLE 26

Methyl
11-(2-piperidinoethylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate (Compound 17)

The desired product is obtained by substituting piperidine for 4-methylpiperazine in Example 22.

EXAMPLE 27

Methyl 11-[2-(4-methylpiperazino)ethylidene]-6,11-dihydrodibenz[b,e]oxepin-2-acetate (Compound 25)

The desired product is obtained by substituting methyl 11-methylene-6,11-dihydrodibenz[b,e]oxepin-2-acetate for methyl 11-methylene-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate in Example 27.

EXAMPLE 28

11-(3-Dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylic acid (Compound 3)

In this example, 26.1 g of methyl 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate is dissolved in a mixed solvent of 500 ml of methanol and 30 ml of water and 6.2 g of sodium hydroxide is added thereto. The mixture is heated at reflux for two hours. After allowing the mixture to stand for cooling, aqueous 4N-hydrochloric acid solution is added thereto to adjust the pH to 7 and the mixture is concentrated under reduced pressure. The concentrate is purified by column chromatography on high porous polymer (HP-20) (eluent: water:methanol = 1:2) to obtain 25.0 g of the desired product.

Cis form white crystal

Melting point: 162–164° C.

NMR (DMSO-d_6, δ, ppm): 2.28(s, 6H), 2.40–2.70(m, 4H).
5.20–5.40(broad, 2H), 5.72(t, 1H, J = 7.0Hz),
6.85–7.90(m, 7H)

IR (KBr disk, cm^{-1}) 3400, 1610, 1370, 1220, 1005

Elemental analysis (%): as $C_{20}H_{21}O_3N.\frac{1}{3}H_2O$

	C	H	N
Found:	73.00	6.67	4.14
Calculated:	72.93	6.63	4.25

Trans form white crystal

Melting point: 242°–244° C.

NMR (DMSO-d_6, δ, ppm) 2.25(s, 6H), 2.40–2.70(m, 4H).
5.20–5.40(broad, 2H), 6.09(t, 1H, J = 7.0Hz).
6.78–7.90(m, 7H)

IR (KBr disk, cm^{-1}) 3400, 1610, 1380, 1222, 1010

Elemental analysis (%):

	C	H	N
Found:	74.30	6.60	4.30
Calculated:	74.28	6.55	4.30

EXAMPLES 29–34

11-(3-Diethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylic acid (Compound 5)

11-(3-Pyrrolidinopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylic acid (Compound 7)

11-(4-Dimethylaminobutylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylic acid (Compound 9)

11-[2-(4-Methylpiperazino)ethylidene]-6,11-dihydrodibenz[b,e]oxepin-2-carboxylic acid (Compound 11)

11-(2-Morpholinoethylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylic acid (Compound 13)

11-(2-Thiomorpholinoethylidene)-6.11-dihydrodibenz[b,e]oxepin-2-carboxylic acid (Compound 15)

These products are obtained by hydrolysis in the same manner as in Example 28.

Compound	Melting point (°C.)	Elementary analysis (%) or Mass spectrum			
5	White solid 120–123 (Acetonitrile)	Cis: Trans = 7:3			
		As $C_{22}H_{25}O_3N$			
			C	H	N
		Found	75.10	7.11	3.87
		Calculated	75.19	7.17	3.99
7	Colorless amorphous About 150 (Decomposition)	For $C_{22}H_{23}O_3N$ 349 (M^-)			
9	White solid 128–129 (Water)	Cis: Trans = 9:1. dihydrate			
		As $C_{21}H_{23}NO_3.2H_2O$			
			C	H	N
		Found	67.61	7.03	4.00
		Calculated	67.54	7.29	3.75
11	White solid 150–153 (Water)	Cis: Trans = 1:9. dihydrate			
		As $C_{22}H_{24}NO_3.2H_2O$			
			C	H	N
		Found	65.98	6.99	6.95
		Calculated	65.98	7.05	7.00
13	White solid 130–133 (Toluene)	Cis: Trans = 1:9			
		As $C_{21}H_{21}O_4N$			
			C	H	N
		Found	71.52	6.11	3.81
		Calculated	71.78	6.02	3.99
15	Colorless amorphous About 140	As $C_{21}H_{21}O_3NS$ 367 (M^-)			

EXAMPLE 35

11-(3-Dimethylaminopropylidene)-6.11-dihydrodibenz[b,e]oxepin-2-acetic acid (Compound 20)

The product is obtained by hydrolysis as in the same manner as in Example 28.

Cis form white crystal

Melting point: 118°–120° C. (Isopropanol)

NMR (DMSO-d_6, δ, ppm): 2.16(s, 6H), 2.30–2.60(m, 4H).
4.04(s, 2H), 5.115(bs, 2H), 5.69(t, 1H, J=7Hz).
6.73–7.40(m, 7H)

Ir (KBr disk, cm^{-1}): 3400, 1580, 1225, 1005

Mass spectrum (m/z): 337 (M^-)

Elementary analysis (%): as $C_{21}H_{23}O_3N$.monohydrate

	C	H	N
Found	70.77	7.36	3.74
Calculated	70.96	7.09	3.94

Trans form white crystal

Melting point: 158°–160° C. (Acetonitrile)

NMR (DMSO-d_6, δ, ppm): 2.05(s, 6H), 2.30–2.60(m, 4H), 4.04(s, 2H), 5.15(bs, 2H), 6.06(t, 1H, J=7Hz), 6.73–7.40(m, 7H)

IR (neat, cm^{-1}): 3380, 1575, 1220, 1005

Mass spectrum (m/z): 337 (M^-)

Elementary analysis (%): as $C_{21}H_{23}O_3N$.monohydrate

	C	H	N
Found	71.06	6.66	3.92

-continued

	C	H	N
Calculated	70.96	7.09	3.94

EXAMPLES 36–39

11-(4-Dimethylaminobutylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid (Compound 22)

11-(3-Pyrrolidinopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid (Compound 24)

11-[2-(4-Methylpiperazino)ethylidene]-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid (Compound 26)

3-[11-(3-Dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-yl]-propionic acid (Compound 28)

These products are obtained by hydrolysis in the same manner as in Example 35. The physicochemical properties are shown in Table 9.

TABLE 9

Compound	Melting point (°C.)	Elementary analysis (%)			
22	White solid 206–209 (Isopropanol)	Cis: Trans = 92:8 as $C_{22}H_{25}O_3N$	C	H	N
		Found	75.20	7.28	4.02
		Calculated	75.19	7.17	3.99
26	White solid 206–209 (Isopropanol)	Cis: Trans = 1:9 as $C_{22}H_{25}O_3N$	C	H	N
		Found	75.19	7.17	3.99
		Calculated	75.15	7.28	3.96

Compound 28

Cis form white crystal

Melting point: 136°–138° C. (Isopropylether)

NMR (DMSO-d_6, δ, ppm): 2.32(m, 2H), 2.38(s, 6H), 2.44–2.56(m, 2H), 2.73(m, 4H), 5.15(bs, 2H), 5.50(m, 1H), 6.7–7.4(m, 7H)

IR (KBr disk, cm^{-1}): 3380, 1645

Mass spectrum (m/z): 351 (M^-)

Elementary analysis (%): as $C_{22}H_{25}NO_3$

	C	H	N
Found	74.83	7.31	3.97
Calculated	75.19	7.17	3.99

Trans form white crystal

Melting point: 148°–149° C. (Acetonitrile)

NMR (DMSO-d_6, δ, ppm): 2.05(s, 6H), 2.24(m, 2H), 2.35(m, 2H), 2.47(t, 2H, J=7.5Hz), 2.72(t, 2H, J=7.5Hz), 4.80–5.50(broad, 2H), 5.99(t, 1H, J=7.1Hz), 6.6–7.5(m, 7H)

IR (KBr disk, cm^{-1}): 3380, 1700

Mass spectrum: 351 (M^+)

Elementary analysis (%): as $C_{22}H_{25}NO_3$.1/5 hydrate

	C	H	N
Found	74.53	7.20	4.32
Calculated	74.42	7.21	3.95

EXAMPLE 40

11-(2-Dimethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid (Compound 37)

The desired product is obtained as a 8:92 mixture of cin-form and anti-form by hydrolysis in the same manner as in Example 27.

White crystal

Melting point: 174°–176° C. (as ½ hydrate)

NMR (DMSO-d_6, δ, ppm): 2.07(s, 6H), 2.30–2.80(m, 4H), 3.47(s, 2H), 4.90–5.30(broad, 2H), 6.74–7.62 (m, 7H)

IR (KBr disk, cm^{-1}): 3350, 1575, 1370, 1010

Elementary analysis (%): as $C_{20}H_{22}N_2O_3 \cdot \frac{1}{2}$ hydrate

	C	H	N
Found	69.47	6.77	8.06
Calculated	69.14	6.67	8.06

EXAMPLES 41–47

11-(2-Diethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-carboxylic acid (Compound 35)

11-(2-Diethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid (Compound 39)

11-(3-Dimethylaminopropyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid (Compound 41)

3-[11-(2-Diethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-yl]-propionic acid (Compound 43)

2-[11-(2-Dimethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-yl]-propionic acid (Compound 45)

11-(2-Dimethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-3-acetic acid (Compound 47)

11-(3-Dimethylaminopropyl)imino-6,11-dihydrodibenz[b,e]oxepin-3-acetic acid (Compound 49)

The desired compounds are obtained by hydrolysis in the same manner as in Example 40. The physicochemical properties are shown in Table 10.

TABLE 10

Compound	Melting point (°C.)	Elementary analysis (%) or Mass spectrum			
35	White solid 198–200 (Isopropyl ether)	Cin: Anti = 1:1 as $C_{21}H_{24}O_3N_2$	C	H	N
		Found	71.66	6.90	7.82
		Calculated	71.57	6.86	7.95
39	White solid 161–162 (Ethyl acetate)	Anti: 98% as $C_{22}H_{26}O_3N_2$	C	H	N
		Found	72.25	7.24	7.58
		Calculated	72.11	7.15	7.64
41	White solid 171–173 (Isopropanol)	Anti: 97% as $C_{21}H_{24}O_3N_2$	C	H	N
		Found	71.35	6.92	7.69
		Calculated	71.57	6.86	7.95
43	Colorless Oily	as $C_{23}H_{28}O_3N_2$ 380 (M^-)			
45	White solid 132–135 (Water)	Anti > 95% as $C_{21}H_{24}O_3N_2$	C	H	N
		Found	71.39	6.99	7.91
		Calculated	71.57	6.86	7.95
47	White solid 194–195 (Decomposition) (Methanol)	Anti > 95% as $C_{20}H_{22}O_3N_2$	C	H	N
		Found	70.87	6.80	7.93
		Calculated	70.98	6.55	8.28

TABLE 10-continued

Compound	Melting point (°C.)	Elementary analysis (%) or Mass spectrum			
49	White solid 174–175 (Decomposition) (Isopropanol)	Anti > 95% as $C_{21}H_{24}O_3N_2$	C	H	N
		Found	71.42	7.03	8.06
		Calculated	71.57	6.86	7.95

EXAMPLE 48

Methyl 11-(3-dimethylaminopropyl)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate (Compound 50) Process A: 11-Hydroxy-2-(4,4-dimethyl-2-oxazoline-2-yl)-6,11-dihydrodibenz[b,e]oxepin

In this process, 2.40 g of 11-oxo-2-(4,4-dimethyl-2-oxazoline-2-yl)-6,11-dihydrodibenz[b,e]oxepin is dissolved in 100 ml of methanol and 0.3 g of sodium borohydride is added thereto. After stirring the mixture at room temperature for 30 minutes, the solvent is distilled away under reduced pressure. The residue is extracted with 200 ml of methylene chloride, washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution in order, and dried over anhydrous sodium sulfate and the solvent is distilled away under reduced pressure. The residue is recrystallized from toluene to obtain 2.06 g of the desired product as a white solid.

Melting point: 201°–203° C.

Process B: 11-(3-Dimethylaminopropyl)-2-[4,4-dimethyl-2-oxazoline-2-yl)-6,11-dihydrodibenz[b,e]oxepin

In this process, 1.90 g of 11-hydroxy-2-(4,4-dimethyl-2-oxazoline-2-yl)-6,11-dihydrodibenz[b,e]oxepin is dissolved in 30 ml of methylene chloride and 0.7 ml of thionyl chloride is added thereto under ice-cooling. After stirring the mixture at room temperature for one hour, the solvent is distilled away under reduced pressure to obtain a crude product of 11-chloro-2-(4,4-dimethyl-2-oxazoline-2-yl)-6,11-dihydrodibenz[b,e]oxepin. The crude product as such is dissolved in 10 ml of tetrahydrofuran without purification.

To the solution is dropwise added under a nitrogen atmosphere 3-dimethylaminopropyl magnesium chloride obtained in the same manner as in Process C of Example 1 until the raw material is used up. The reaction mixture is extracted with 100 ml of methylene chloride, washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution in order and dried over anhydrous sodium sulfate, and the solvent is distilled away under reduced pressure. The residue is purified by column chromatography on silica gel (eluent: hexane:ethyl acetate:triethylamine = 10:10:1) to obtain 0.06 g of the desired product as a colorless oily matter.

Mass spectrum (m/z): 378 (M^+) for $C_{24}H_{30}O_2N$

Process C: Methyl 11-(3-dimethylaminopropyl)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate

In this process, 60 mg of 11-(3-dimethylaminopropyl)-2-(4,4-dimethyl-2-oxazoline-2-yl)-6,11-dihydrodibenz[b,e]oxepin is dissolved in a mixed solvent of 20 ml of water and 20 ml of dioxane and 10 mg of p-toluenesulfonic acid is added thereto. After heating the

mixture at reflux for 3 hours, the mixture is concentrated under reduced pressure. The concentrate is extracted with 100 ml of ethyl acetate, washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution in order and dried over anhydrous sodium sulfate, and the solvent is distilled away under reduced pressure. The residue is dissolved in a mixed solution of 30 ml of methanol and 10 ml of aqueous 1N-sodium hydroxide solution and the mixture is heated at reflux for 2 hours. After allowing the mixture to stand for cooling, the pH of the mixture is adjusted to 5.4 with aqueous 4N-hydrochloric acid solution.

The solvent is distilled away under reduced pressure and the residue is redissolved in 50 ml of methanol. After adding 10 mg of p-toluenesulfonic acid thereto, the mixture is heated at reflux for 3 hours and concentrated under reduced pressure. The residue is extracted with 100 ml of ethyl acetate, washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution in order and dried over anhydrous sodium sulfate and the solvent is distilled away under reduced pressure. The residue is developed on 3 sheets of preparative TLC (20 cm $\times$20 cm $\times$0.25 mm) with a mixed solvent (eluent: hexane:ethyl acetate:triethylamine = 10:10:2). The band at R_f=0.47 is collected, and extracted with methylene chloride and the solvent is distilled away under reduced pressure to obtain 5.3 mg of the desired product as a colorless oily matter.

NMR ($CDCl_3$, δ, ppm): 1.20–1.40(m, 1H), 1.60–1.80 (m, 2H), 2.18(m, 2H), 2.56(s, 6H), 2.74(dd, 2H, J=6.6Hz and 9.5Hz), 3.90(s, 3H), 5.00 and 5.59 (ABq, 2H, J=14.2Hz), 6.96–7.88(m, 7H)

Mass spectrum (m/z): 325 (M^-) for $C_{20}H_{23}O_3N$

IR (neat, ν, cm^{-1}): 3400, 1710, 1610, 1110

EXAMPLE 49

½ Fumarate .1/5 hydrate of Compound 3 (Compound 3')

In this example, 3.95 g of 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylic acid (Compound 3) is dissolved in 100 ml of acetone and 1.42 g of fumaric acid is added thereto. The mixture is stirred at room temperature. The deposited crystals are recovered by filtration and recrystallized from isopropanol to obtain 4.15 g of the desired product as a white solid.

Melting point: 253°–254° C.

Isomer purity: Trans form 99% (measured by HPLC)

Elementary analysis (%): as $C_{20}H_{21}NO_3.\frac{1}{2}C_4H_4.1/5H_2O$

	C	H	N
Found	68.74	6.35	3.61
Calculated	68.63	6.13	3.64

EXAMPLES 50–59

The products identified in Table 11, the physicochemical properties of which are shown in Table 12 are obtained in the same manner as in Example 49.

TABLE 11

Compound No.		
5'	Monofumarate · 1/3 hydrate of Compound 5	(Cis form 99%)
7'	Monofumarate · monohydrate of Compound 7	(Cis form 70%)
11'	Difumarate · 1/2 hydrate of Compound 11	(Trans form 100%)
13'	1/2 Fumarate · 1/2 hydrate of Compound 13	(Trans form 93%)
15'	Monofumarate of Compound 15	(Trans form 100%)
20'	Monofumarate · 3/2 hydrate of Compound 20	(Trans form 95%)
26'	Monofumarate · 2/3 hydrate of Compound 26	(Trans form 88%)
28'	Monofumarate · 1/2 hydrate of Compound 28	(Trans form 63%)
31'	1/2 Fumarate · monohydrate of Compound 31	(Trans form 95%)
33'	Monofumarate of Compound 33	(Cis form 100%)

TABLE 12

Compound	Melting point (°C.)	Elementary analysis (%)			
5'	White solid	as $C_{26}H_{29}O_7N.1/3H_2O$			
	100		C	H	N
	(Decomposition)	Found	66.03	6.31	2.96
	(Isopropylether)	Calculated	66.14	6.55	3.14
7'	White solid	as $C_{26}H_{27}O_7N.H_2O$			
	vague owing to		C	H	N
	absorption of	Found	64.32	6.11	2.66
	moisture	Calculated	64.59	6.05	2.90
11'	White solid	as $C_{30}H_{32}O_{11}N_2.1/2H_2O$			
	266–268		C	H	N
	(Isopropanol)	Found	59.55	5.44	4.53
		Calculated	59.50	5.49	4.63
13'	White solid	as $C_{23}H_{23}O_6N.1/2H_2O$			
	232–235		C	H	N
	(Decomposition)	Found	66.63	5.83	3.44
	(Isopropanol)	Calculated	66.72	5.85	3.44
15'	White solid	as $C_{25}H_{25}O_7NS$			
	250–254		C	H	N
	(Isopropanol)	Found	64.21	5.59	3.73
		Calculated	64.23	5.39	3.99
20'	White solid	as $C_{25}H_{27}O_7N.3/2H_2O$			
	135–138		C	H	N
	(Isopropyl	Found	62.58	6.12	2.77
	ether)	Calculated	62.49	6.29	2.91
26'	White solid	as $C_{27}H_{30}O_7N_2.2/3H_2O$			
	108–110		C	H	N
	(Isopropanol)	Found	64.15	6.47	5.24
		Calculated	64.02	6.24	5.53
28'	White amorphous	as $C_{26}H_{29}NO_7$			
	vague owing to		C	H	N
	absorption of	Found	66.58	6.61	2.82
	moisture	Calculated	66.80	6.25	3.00
31'	White solid	as $C_{23}H_{27}O_4N.H_2O$			
	vague owing to		C	H	N
	absorption of	Found	65.53	6.81	2.96
	moisture	Calculated	65.39	6.92	3.32
	(Petroleum ether)				
33'	White solid	as $C_{26}H_{31}O_6N$			
	146		C	H	N
	(Acetone)	Found	68.81	7.16	3.22
		Calculated	68.86	6.89	3.09

EXAMPLE 60

Monosodium salt.monohydrate of Compound 35 (Compound 35')

In this example, 1.00 g of 11-(2-diethylaminoethyl-)imino-6.11-dihydrodibenz[b.e]oxepin-2-carboxylic acid (Compound 35) is dissolved in 100 ml of methanol and 5.5 ml of 28% sodium methoxide methanol solution is added thereto. After stirring the mixture for one hour, the solvent is distilled away under reduced pressure. The residue is triturated by adding isopropylether and is recovered by filtration to obtain 0.98 g of the desired product as a white solid.

Melting point: vague owing to absorption of moisture
Ratio of isomer: Cin:Anti = 1:1
Elementary analysis: as $C_{21}H_{25}O_4N_2Na.H_2O$

	C	H	N
Found	64.23	6.62	7.01
Calculated	64.27	6.68	7.14

EXAMPLES 61 and 62

The same procedures as in Example 60 are repeated to obtain the products identified in Table 13, the physicochemical properties of which are shown in Table 14.

TABLE 13

Compound No.					
43'	Sodium salt of Compound 43	(Anti form 98%)			
45'	Sodium salt · monohydrate of Compound 45	(Anti form 99%)			
	Melting point (°C.)	Elementary analysis (%)			
43'	White solid vague owing to	as $C_{23}H_{27}O_3N_2Na$	C	H	N
	absorption of moisture	Found	68.46	7.00	6.88
		Calculated	68.64	6.76	6.96
45'	White solid 140–145	as $C_{21}H_{25}O_3N_2Na.H_2O$	C	H	N
	(Isopropyl ether)	Found	64.11	6.57	6.99
		Calculated	64.27	6.42	7.14

EXAMPLE 63

Tablet

A tablet comprising the following components is prepared in a conventional manner.

Trans-11-(3-dimethylaminopropylidene)-6.11-dihydrodibenz[b.e]oxepin-2-carboxylic acid · 1/2 fumarate · 1/5 hydrate (Compound 3'):	30 mg
Lactose:	60 mg
Potato starch:	30 mg
Polyvinyl alcohol:	2 mg
Magnesium stearate:	1 mg
Tar pigment:	q.s.

EXAMPLE 64

Powder

A powder comprising the following components is prepared in a conventional manner.

Trans-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid · monofumarate · 3/2 hydrate (Compound 20'):	30 mg
Lactose:	270 mg

EXAMPLE 65

Syrup

A syrup comprising the following components is prepared in a conventional manner.

11-(2-dimethylaminoethyl)imino-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid (Compound 37):	300 mg
Purified sucrose:	40 g
Methyl p-oxybenzoate:	40 mg
Propyl p-oxybenzoate	10 mg
Strawberry flavor:	0.1 cc
Water is added to the above components until the total valume becomes 100 cc	

EXAMPLE 66

Methyl 11-(3-morpholinopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate (Compound 55)

The desired product is obtained by substituting (3-morpholinopropyl)-triphenylphosphonium bromide hydrobromide for (3-dimethylaminopropyl)-triphenylphosphonium bromide hydrobromide in Example 5 as a colorless oily matter.

Mass spectrum (m/z): 379 (M^+) for $C_{23}H_{25}O_4N$

EXAMPLE 67

Methyl 11-(3-thiomorpholinopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylate (Compound 57)

The desired product is obtained by substituting (3-thiomorpholinopropyl)-triphenylphosphonium bromide hydrobromide for (3-dimethylaminopropyl)-triphenylphosphonium bromide hydrobromide in Example 5 as a colorless oily matter.

Mass spectrum (m/z): 395 (M^+) for $C_{23}H_{25}O_3NS$

EXAMPLE 68

Methyl trans-3-[11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-yl]-acrylate (Compound 59)

The desired product is obtained by substituting trans-3-(11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-yl)-acrylic acid for 11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid in Example 9 as a colorless oily matter.

Mass spectrum (m/z): 363 (M^+) for $C_{23}H_{25}O_3N$

EXAMPLE 69

Methyl 11-(3-methylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetate (Compound 61)

The desired product is obtained by substituting (3-methylaminopropyl)-triphenylphosphonium bromide hydrobromide for (3-dimethylaminopropyl)-triphenylphosphonium bromide hydrobromide in Example 9 as a colorless oily matter.

Mass spectrum (m/z): 337 (M^+) for $C_{21}H_{23}O_3N$

EXAMPLE 70

Methyl 11-(3-aminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetate (Compound 63)

The desired product is obtained by substituting (3-aminopropyl)-triphenylphosphonium bromide hydrobromide for (3-dimethylaminopropyl)-triphenylphosphonium bromide hydrobromide in Example 9 as a colorless oily matter.

Mass spectrum (m/z): 323 (M^+) for $C_{20}H_{21}O_3N$

EXAMPLES 71-75

11-(3-Morpholinopropylidene)-6,11-dihydrodibenz[b,e]-oxepin-2-carboxylic acid (Compound 56)

11-(3-Thiomorpholinopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-carboxylic acid (Compound 58)

Trans-3-[11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-yl]-acrylic acid (Compound 60)

11-(3-Methylaminopropylidene)-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid (Compound 62)

11-(3-Aminopropylidene)-6,11-dihydrodibenz[b,e]-oxepin-2-acetic acid (Compound 64)

The same hydrolysis procedures as in Example 28 are repeated to obtain the desired products, the physicochemical properties of which are shown in Table 15.

TABLE 15

Compound	Melting point (°C.)	Elementary analysis (%) or Mass spectrum			
56	White solid 130-131 (Decomposition) (Isopropanol)	Cis form 87% as $C_{22}H_{23}O_4N.C_3H_8O$	C	H	N
		Found	70.65	7.34	3.27
		Calculated	70.57	7.34	3.29
58	White solid 201-205 (Isopropanol)	Cis form 87% 1/2 hydrate as $C_{22}H_{23}O_3NS.1/2H_2O$	C	H	N
		Found	67.69	6.03	3.36
		Calculated	67.67	6.20	3.59
60	Colorless oily matter	394 (M^+) for $C_{22}H_{23}O_3N$			
62	White solid	Cis form 100%			

TABLE 15-continued

Compound	Melting point (°C.)	Elementary analysis (%) or Mass spectrum			
	230–238 (Water)	as $C_{20}H_{21}O_3N$			
			C	H	N
		Found	74.01	6.60	4.01
		Calculated	74.28	6.55	4.33
64	White solid 250 (Decomposition) (Water)	Cis form 100% as $C_{19}H_{19}O_3N$			
			C	H	N
		Found	73.57	6.38	4.44
		Calculated	73.77	6.19	4.53

EXAMPLE 76

Cis form of monofumarate of Compound 60 (Compound 60') is obtained in the same manner as in Example 49 as a white solid.

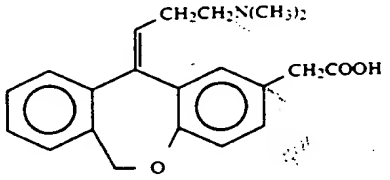
Melting point: 176°–178° C. (Isopropanol)

Elementary analysis (%): as $C_{26}H_{27}O_7N$

	C	H	N
Found	67.09	5.97	2.89
Calculated	67.09	5.85	3.01

What is claimed is:

1. A dibenz[b,e]oxepin compound in cis form having the formula



and pharmaceutically acceptable salts thereof.

2. A compound according to claim 1, wherein said salt is selected from the group consisting of acid addition salt, metal salt, ammonium salt, organic amine addition salt, and amino acid addition salt.

3. A pharmaceutical composition comprising a pharmaceutical carrier and as an active ingredient, an effective amount of a dibenz[b,e]oxepin compound defined in claim 1.

* * * * *

APPENDIX F

Maintenance Fee Statement

UNITED STATES DEPARTMENT OF COMMERCE
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MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 10, "status" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 10, "status" below. An explanation of the codes appears on the reverse of the Maintenance Fee Statement. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITM NBR	PATENT NUMBER	FEE CDE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	5,116,863	183	960	----	07/020,900	05/26/92	03/02/87	04	NO	PAID

If the "status" column for a patent number listed above does not indicate "PAID" a code or an asterisk (*) will appear in the "status" column. Where an asterisk (*) appears, the codes are set out below by the related item number. An explanation of the codes indicated in the "status" column and as set out below by the related item number appears on the reverse of the maintenance fee statement.

ITM NBR	ATTY DKT NUMBER
1	5.1022

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